Hemispheric differences in the control of finger tapping

vom Fachbereich Biologie der Technischen Universität Darmstadt

zur Erlangung des Grades
Doctor rerum naturalium
(Dr. rer. nat.)

Dissertation
von Anja Pflug

Erstgutachter: Prof. Dr. Ralf Galuske
Zweitgutachter: PD Dr. Konstantin Rothkopf
Drittgutachter: PD Dr. Christian A. Kell

Darmstadt 2019

Pflug, Anja: Hemispheric differences in the control of finger tapping
Darmstadt, Technische Universität Darmstadt,
Jahr der Veröffentlichung der Dissertation auf TUprints: 2020
URN: urn:nbn:de:tuda-tuprints-114207
Tag der mündlichen Prüfung: 22 Januar 2020

Das menschliche Gehirn ist eine großartige Sache:
es funktioniert vom Augenblick der Geburt an - bis zu dem Moment,
wo man aufsteht, eine Rede zu halten (Mark Twain).

Für Emma Luise und Paul Mattis

Acknowledgements

The research presented in this thesis was carried out at the neurological hospital Frankfurt in collaboration with the MEG Unit in the Brain Imaging Center of the Goethe University in Frankfurt.
I would like to thank PD. Dr. Christian Kell for the supervision of my thesis. Working with him was always a pleasure, since he was open for all my thoughts and channeled them into fruitful directions. He gave me the opportunity to plan my work independently in collaboration with internal and external co-workers. Thanks to him, I also had the opportunity to join awake brain surgeries and invasive recordings in epileptic patients.
I also thank Prof. Dr. Ralf Galuske for being my supervisor at the technical university of Darmstadt and PD Dr. Constantin Rothkopf for agreeing to be co-supervisor of this thesis.
A special thanks goes to my PhD partner Florian Gompf with whom I planned the details of the experiments. Having him as a ping-pong parter with bilateral dependencies helped both of us staying focused. With his calm and friendly way he always was a huge source of motivation and we trusted each other blindly (even in the selection of accommodations for conferences).
I thank Michael Wibral for his motivational support and for his perfect way to explain complex mechanisms. There should be more people like you in science.
Thanks to the members of the Freq-Club we founded on the way (Alla Brodski, Georg Paasch and Anna Oliynyk). Our weekly sessions deepened the understanding of the methods with a lot of fun. Thank you for the time we spent together. I thank Bastian Hagel for the implementation of the second motor paradigm. This one year of preparation was challenging but due to the fluent and cooperative workflow between me, you and Florian this program is now nice to be used by many members of our group. I would like to

thank the whole brainclocks group for the years we spent together sharing room, thoughts, food and parties. Special thanks goes to Marion Behrens for open ears and calm words in good and bad times, as well as for Johannes Gehrig and Johann Zoellner for the technical introduction into the invasive recordings. I thank my coauthor Muthuraman Muthuraman for the fluent cooperation between Frankfurt and Mainz showing me the optimal analysis strategy for the MEG data.

Writing a thesis is never easy and the contribution of family and friends can only be underestimated. This thesis would have never been doable without the help of my husband Ulrich Pflug who always kept my back free, patiently endured all my moods and quirks and forced me to focus. Thank you a lot! Thanks also to my parents and my sister for taking care of us in critical situations and for believing in me finishing this thesis.

Summary

The human brain is composed of two hemispheres. Even though most functions are represented in both, they differ in processing abilities, enabling the left hemisphere to speak and control learned motor sequences. One current hypothesis how the hemispheres differ is in their processing of relative frequencies of sensory stimuli (Ivry and Robertson, 1998; Flevaris et al., 2010). The Double-filtering-by-frequency (DFF) theory proposes that the left hemisphere has a preference to process relavtive high frequencies and the right hemisphere relative low frequencies. The authors hypothesize that, hemispheric differences in sensory processing should transfer to the speech and motor domain. The goal of this thesis was to investigate frequency dependent hemispheric preferences for hand motor control. An fMRI and an MEG experiment were performed to answer the following questions: Is there a hemispheric preference for relative movement frequencies visible in behavioral measures? What are the cortical areas and neural mechanisms involved explaining possible preferences? In a first auditory paced finger tapping study (Pflug et al., 2017) we investigated whether the left and the right hand differ in their temporal precision to tap relative slow and fast rhythms. While the fast tapping rate was defined in tapping to every beat of a sequence of auditory beats, the slow tapping rate differed between two experimental groups. While the first group tapped a standard quadruple meter (tap on beat position one), the second group had to tap a syncopated quadruple meter (tap on beat position four). Participants were asked to tap either bimanual monofrequent (fast or slow) or multifrequent (one hand fast, the other slow). As predicted by the DFF-theory, the right hand was more precise when tappings the fast rate, while the left hand performed better during slow tapping. This effect was found only in the group tapping the

syncopated rhythm, suggesting that frequency-dependent lateralization can be masked in case the two rhythms can be interpreted in a hierarchical Gestalt as in the standard quadruple meter.

To investigate frequency-dependent lateralization further, syncopated slow tapping was compared with fast tapping during fMRI and MEG. The internal generation of a slow rhythm increased BOLD activity in the SMA and in the right auditory association cortex (A2). MEG revealed that the right A2 represented the slow tapping more strongly compared to the left A2 in an amplitude modulation of low beta power. In contrast, the left A2 represented the fast auditory beat rate more strongly than the right A2, although, both cortices received the same auditory input. These results identify the sensory cortices as the source of lateralization of hand motor control and validate the DFF-hypothesis. The motor cortices represented only the rhythm of the motor output in an amplitude modulation of low beta oscillations with a non-linear relationship between beta power and BOLD activity.

Finally, effective connectivity analysis of auditory-motor interactions revealed that stronger bidirectional auditory-motor coupling in the left compared to the right hemisphere could privilege the left cerebral hemisphere for rhythm integration in a hierarchical Gestalt. This could represent a mechanism explaining at least in part left lateralized speech processing.

Contents

List of Figures

List of Tables

List of Acronyms

BOLD Blood Oxygen Level Dependent

DFF Double-Filtering-by-Frequency theory

dPMC dorsal premotor cortex

EEG Electroencephalography

ECoG electrocorticography

EMG Electromyogram

fMRI functional Magnetic Resonance Imaging

GMP Generalized Motor Program

MEG Magnetencephalography

sEEG stereoelectroencephalography

SMA supplementary motor area

SQUIDs superconducting quantum interference devices

List of publications with contributions

1. *Pflug, A., Gompf, F. & Kell, C.A. (2017) Bimanual tapping of a syncopated rhythm reveals hemispheric preferences for relative movement frequencies. Human movement science, 54:287-296.*
   Contributions: AP - study design, recruitment of participants, data acquisition, design and implementation of analysis pipeline, data analysis and writing of the manuscript; FG - study design and manuscript revision; CAK - study design, supervision of data analysis and writing of the manuscript.

2. *Gompf, F., Pflug, A., Laufs, H. & Kell, C.A. (2017) Nonlinear Relationship between BOLD Activation and Amplitude of Beta Oscillations in the Supplementary Motor Area during Rhythmic Finger Tapping and Internal Timing. Frontiers in Human Neuroscience, 11:582.*
   Contributions: FG - study design, data acquisition, data analysis and writing of the manuscript; AP - study design, recruitment of participants, data acquisition, data analysis and writing the manuscript; HL - provision of the EEG-fMRI equipment, methodological support for EEG-fMRI data acquisition and analysis and manuscript revision; CAK - study design, supervision of data analysis and writing of the manuscript.

3. *Pflug, A., Gompf, F., Muthuraman, M., Groppa, S. & Kell, C.A. (2019) Differential contributions of the two human cerebral hemispheres to action timing. elife, 8:e48404*
   Contributions: AP - study design, recruitment of participants, data acquisition, data analysis and writing of the manuscript; FG - study design, data acquisition, data analysis and writing of the manuscript; MM - provision of novel statistical tool (TPDC) and description of this in the manuscript; SG - study design and manuscript revision; CAK - study design, supervi-

sion of data analysis and writing of the manuscript.

All published material has been reproduced with permission from the publisher.

1 General introduction

1.1 One brain – two hemispheres

The mammalian brain is composed of two cerebral hemispheres which at a first glance look quite symmetric. Both are connected via a huge fibre bundle - the corpus callosum. For a long time scientists believed that functions are distributed equally over the hemispheres. However, when Broca discovered the co-occurrence of left hemispheric damage and aphasia 150 years ago (for a translation of the original french paper see Berker et al. (1986)), this view has changed. Since then scientists have shown more and more evidence that there is something special about the left hemisphere. Not only is this hemisphere hosting the main faculty of speech production (Wada et al., 1975; Branch et al., 1964), but also seems to be piloting movement control (Kimura, 1993). Surprisingly, in humans 85 percent of the population is right handed and the control of the right limbs is controlled by the left hemisphere, pointing to a specific role of the left hemisphere in both, speech production and hand motor control.

The concept that a given function is mainly represented in one half of the brain is called hemispheric specialization or hemispheric dominance (Tzourio-Mazoyer, 2016). A milder form where one function is pronounced in one hemisphere is called lateralization. When calling the left hemisphere dominant, it indicates a minor role of its right counterpart. This implies, that when separating the hemispheres, the right hemisphere should not be able to perform tasks independently.

1.1.1 Cutting connections

Since the 1950s the dogmatic view of the dominant left and non-dominant right hemisphere changed with observations in split-brain

patients. In those patients, the corpus callosum was cut to prevent a spread of epileptic seizures from one hemisphere to the other. With this surgery, the direct inter-hemispheric communication pathways were destroyed which lead to changes in behavior that challenged the concept of a clear left hemispheric dominance. Beside a right hemisphere specialization for attention and visuospatial processing (McFie et al., 1950), each hemisphere was able to control motor output independently (Franz et al., 1996; Gazzaniga, 2000). In neuropsychological experiments, patients were asked to draw lines either using symmetric bimanual movements, in which the limbs performed the same spatial trajectory or using asymmetric bimanual movements in which the spatial pattern between the limbs differed (see Figure 1.1). While healthy subjects showed interference between the two hands in the asymmetric movements, split brain patients were able to perform both movement types without interference. While split-brain patients showed advantages for controlling asymmetric spatial movements, when tested in asymmetric finger-tapping paradigms, they were unable to tap bimanual rhythms which were not in phase or in perfect antiphase (180°). This shows that an intact corpus callosum is necessary for controlling timing demands for hand movements (Tuller and Kelso, 1989).

Since experiments with split-brain patients have shown that the right hemisphere is capable of processing information individually, new ideas on hemispheric lateralization emerged with an explosion of new hypotheses on how the hemispheres differ in functionality. More obscure hypotheses like the left hemisphere is logic and analytic while the right is emotional and creative (for a critical review see Corballis (2014)) stand next to more serious hypotheses, which formulate more general frameworks based on the assumption that cortical functions are distributed over both hemispheres with specific

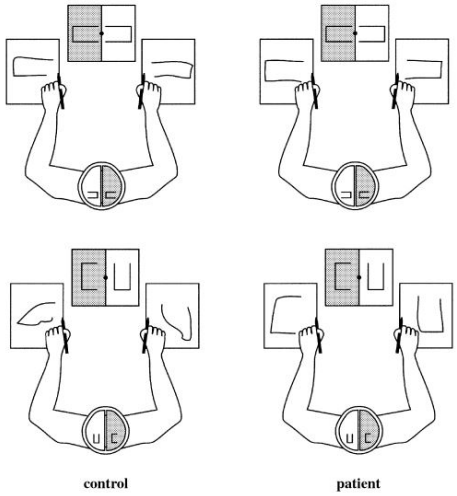

Figure 1.1: The task of drawing two rectangles is similar for healthy controls and split-brain patients when the spatial features of the movement path are symmetric (top figures). However, when the spatial features are diverging between the hand movements (bottom figures), split-brain patients are still able to perform these movements without interference. The inference in healthy subjects is related to inter-hemispheric cross-talk (from Franz et al. (1996)).

preferences. One mayor hypothesis of those is the Double-Filtering-by-Frequency theory (DFF), in which this work is embedded.

1.1.2 The two sides of perception

In 1986, physiologists noticed an effect when asking stroke patients to reproduce Navon patterns (Delis et al., 1986), pictures which are composed of global and local features (e.g. a letter represented of different smaller letters, Navon (1977)). While patients with a left hemispheric stroke were not able to reproduce local features, right hemispheric stroke patients were unable to reproduce global features of the shown stimulus (see figure 1.2). The results were interpreted as a left hemispheric processing of local stimulus features and a right hemispheric processing of global features, which were unaccessible in case of tissue damage. Lesions in these patients were located at the temporal-parietal junctions, a critical region for sensory-motor

transformations.

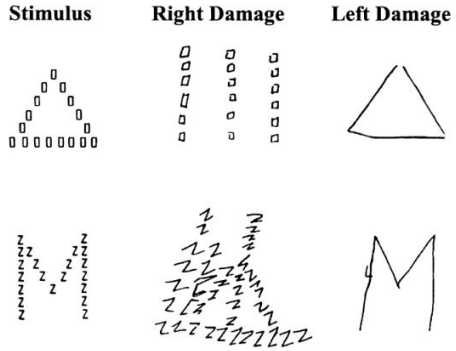

Figure 1.2: Patients were asked to reproduce the Navon patterns shown on the left side. Patients with a right hemispheric damage could not reproduce the global shape and patients with a left hemispheric damage could not reproduce the local shape of the stimulus (from Delis et al. (1986)).

To test this phenomenon in healthy subjects, gratings with different frequencies were used within a visual discrimination paradigm where stimuli were flashed only in one visual hemifield (Kitterle et al., 1990). In the visual system, information from each hemifield is separately processed. Differences in reaction times were in line with observations from stroke patients. Even though global features were faster detected than local features, reaction times were shorter, when global features were presented in the left visual hemifield (right cerebral hemisphere). For local features, reaction times were shorter when stimuli were presented in the right visual hemifield (left cerebral hemisphere). To investigate further, visual gratings with different spatial frequencies were tested in discrimination experiments (Kitterle et al., 1990), revealing the same effects. As long as subjects had to identify the relative higher or lower frequency, results indicated hemispheric preferences for spatial frequencies.
In the auditory domain, information from one ear reaches both auditory cortices. However, the majority of fibers target the contra-

lateral hemisphere, which enables scientists to investigate hemispheric preferences by using dichotic stimulation. This paradigm allows investigating functional lateralization using two different auditory inputs within the two ears. Words were better identified, when they were presented in the right ear, a phenomenon which is called the right ear advantage (Berlin et al., 1973; Shankweiler and Studdert-Kennedy, 1967). On the other hand, melodies were better identified when presented to the left ear (Shankweiler, 1966; Kimura, 1964). In a controlled experiment, using tones with different frequencies (Ivry and Lebby, 1993). These results and more recent ones (Flinker et al., 2019) indicate that, not only in the visual system but also in the auditory system, the processing of relative frequencies of stimuli is different within the two hemispheres. In their book Ivry and Robertson (1998) enroll a general framework for the lateralized processing of information. They describe a two-stage process: in the first stage an attentional filter sets a frequency range in which the stimulus of interest is located (selective attention). If the stimulus is complex, relative high and low frequencies are separated between the hemispheres with a left hemispheric preference for high frequent stimulus features and a right hemispheric preference for low frequent stimulus features.

The two stages of the DFF (Ivry and Robertson, 1998)
1) Selective filtering of task relevant information
2) Asymmetric filtering of cerebral hemisphere (left high & right low frequencies)

Hemispheric preferences for relative frequencies were found in perceptual tasks. However, since sensory and motor functions are highly coupled in the human cortex the authors proposed that these asymmetries should also be present in output functions like speech control and motor processes. The latter one is investigated in this

work.

1.1.3 Lateralization of motor functions

A way to investigate relative hemispheric preferences in motor control is to use bimanual movements. However, the left hemisphere is dominant in motor control (Kimura, 1993; Haaland et al., 2004) and a stroke in this hemisphere induces handicap in both hands. This suggests that the left hemisphere hosts motor plans for both hands, which would produce a right hand bias when testing the proposed preferences in bimanual tasks. Here, an appropriate selection of task is required to reveal hemispheric preferences. Like in the sensory domain where multi-frequent, non-integrated stimuli (like big letters built out of small letters) were used, movement rates of both hands should not be integrated into a learned movement pattern. How exactly the two hands are coordinated in bimanual movements is still a question of debate. Some results suggest that one Generalized Motor Program (GMP) could exist for coordinating movements of both hands. In this case, revealing hemispheric preferences would be impossible. Other results rather indicate that each hand is controlled independently by the respectively contralateral hemisphere, which is also in line with the observations in split brain patients who can perform movements independently per hand. However, even assuming two independent "motor programs", interference between both hands is observed when performing asymmetric movements as described earlier (see section 1.1.2 and figure 1.1). Hemispheric crosstalk over the corpus callosum is thought as origin of these interferences (Gazzaniga, 2000), but it also enables tempo-spatial coordination of both hands for example when playing a musical instrument (Gerloff and Andres, 2002) or tying shoes.

1.2 Testing the DFF in bimanual actions

The major goal of this thesis was to test if it would be possible to reveal hemispheric preferences in for relative frequencies also in the motor domain and if yes, to identify cortical areas involved. To start with, we had to define the term "movements" with relative frequencies. This can be done in two ways: either the movement type is kept constant and the temporal rate in which the movement is performed is altered, or movements differ in their spatiotemporal pattern with one movement being faster than the other. To test both options, we investigated two different bimanual paradigms. To investigate constant movements with different temporal frequencies, a bimanual finger tapping task was used. To investigate different speeds of movements, a visually controlled pressure sensor manipulation task was selected. In this thesis only the results of the first experiment will be reported and in the following be described in more detail. For the sake of completeness all experiments and methods used within the scope of this theses are shortly listed.
In the paradigm, a bimanual finger tapping task was used to keep the actual movement type constant but to experimentally manipulate the rate of the movement. Participants had to tap to a continuous auditory beat either to every occurring beat, representing the fast tapping rate or only to every fourth beat, representing the slow tapping rate (see Figure 1.3). Tapping was performed unimanual (as control conditions) as well as bimanual mono- and multifrequent. In all conditions the stimulus was the same.

In this thesis, different electrophysiological and imaging methods were combined to get a deeper understanding of the mechanisms used by the two hemispheres to process relative frequencies in movements. Beside identifying the involved cortical and subcortical brain regions, we were also interested how these regions behave and inter-

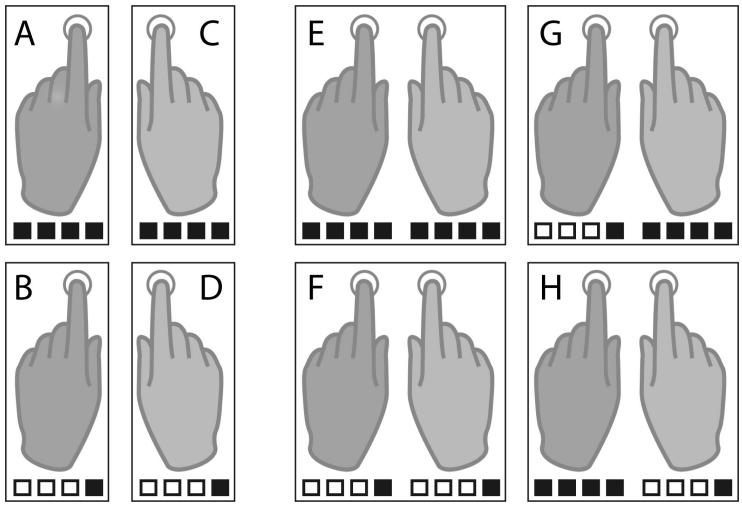

Figure 1.3: Conditions performed in the finger tapping paradigm. Four black squares represent the fast tapping rate in which participants tapped to every single beat of a continuous auditory beat. Three white and one black square represent the slow tapping rate in which participants tapped only to every fourth beat of the continuous auditory stimulation. While in conditions A-F only one frequency is tapped (monofrequent), in condition G and H different rates are tapped by the two hands (multifrequent). Assuming hemispheric preferences with a left hemispheric preference for fast and a right hemispheric preferences for slow tapping rate hand arrangements are either optimal (G) or non-optimal (H) in right-handed participants.

act in time. Figure 1.4 gives an overview about the used methods and the number of recorded datasets. While Magnetencephalography (MEG) and functional Magnetic Resonance Imaging (fMRI) recordings are non-invasive methods and were recorded in healthy participants, stereoelectroencephalography (sEEG) and electrocorticography (ECoG) are invasive methods and were recorded in patients. The different recording techniques were split between two PhD students, Florian Gompf (candidate of medicine) and myself (diplom biologist). The fMRI recordings were measured by Florian Gompf. I recorded the MEG data as well as the invasive data with the help of neurologists and neurosurgeons. To enable a translation from the different methods, the non-invasive measurements and

some of the invasive measurements were combined with Electroencephalography (EEG). Pressure of the tapping finger was always recorded to investigate motor output.

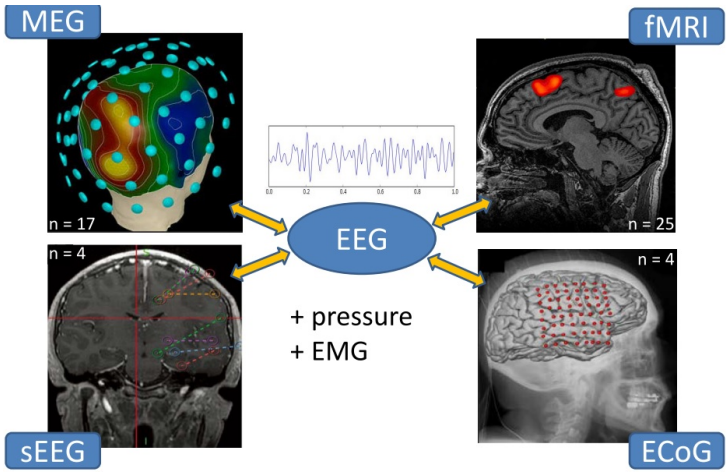

Figure 1.4: Overview of methods used in the project. In all MEG, fMRI and sEEG recordings as well as in one ECoG recording EEG was acquired in parallel. EMG of left and the right extensor digitorum communis muscle was recorded in MEG, fMRI and ECoG recordings. Numbers in the figures indicate the number of successful recordings in the finger tapping paradigm.

The methods were used since they measure different temporal and spatial features of the underlying neural processes. FMRI detects the differences in magnetic resonance spectra of oxygenated and deoxygenated hemoglobin molecules to infer activation (Blood Oxygen Level Dependent (BOLD)). The assumption behind this is that higher neuronal activation leads to an increased oxygen consumption correlated with an increase in the amount of oxygenated blood supplied to this area. The fMRI has a high spatial resolution (millimeter range) and is optimal for identifying brain regions activated in condition contrasts. However, the temporal resolution of the fMRI lies in the second range and cannot be used to reveal temporal dynamics. In the MEG, the magnetic fields orthogonal to

the electric currents in the brain (mostly dendritic current flow) are measured in millisecond precision with superconducting quantum interference devices (SQUIDs). Using beamforming to reconstruct the cortical sources of the recorded magnetic fields enables a spatial resolution of one centimeter. In both methods, EEG was recorded in parallel. In EEG, the electric current flow of the brain is measured with electrodes placed on the scalp.
Invasive recordings were acquired in two groups - tumor patients and patients with focal epilepsy. The focus in this thesis lies on the non-invasive recordings.

1.3 Expected outcomes

1.3.1 Expected outcomes in behavioral parameters

When participants tapped on pressure sensors, there were multiple behavioral features which could be extracted. Not only the tapping accuracy reflected in inter-tap-interval stability could be tested, additionally pressure differences for all conditions could be investigated. Assuming a right hemispheric preference for low and a left hemispheric preference for high relative frequencies, performance should be more accurate in timing with the left hand when tapping slowly and the right hand when tapping fast, respectively. Additionally, participants should be more prone to errors when hemispheric preferences are violated (left hand taps fast, right hand taps slowly). The preferences should translate not only to the accuracy measures but also to the structure of the pressure data. We expect to find a higher representation of the slower rhythm, related to an increased pressure, when tapping with the left hand and higher pressure when the right hand taps fast. In the multifrequent tapping conditions participants should use more pressure when the preferences are respected than when they are violated since higher pressure is negatively correlated to uncertainty.

1.3.2 Expected outcomes in neural parameters

Throughout the experiments we focused mainly on two contrasts. The first one is contrasting the monofrequent fast and slow condition. This compares a condition (fast) in which the participants had to perform an auditory-motor synchronization (external timing, see box below), with a condition in which an internal, not paced, slower rhythm had to be generated. Since in both conditions the same auditory stimulus was presented, external timing was used in both conditions. The fast tapping condition entailed more movement compared to the slow tapping condition. Therefore, the fast tapping should increase the oxygen consumption in the primary motor cortices and should lead to a higher activation in BOLD and a decrease in the beta band power (measured with MEG). Since both conditions used external pacing, we did not expect to find higher activation in areas related to external timing like dorsal premotor cortex (dPMC) in any contrast. Slow tapping should lead to an activation of the supplementary motor area (SMA) and other cortical areas related to internal timing (see box below). When assuming hemispheric preferences for relative frequencies, we expect an additional activation in the right hemisphere for slow tapping. The electro-physiological recordings should reveal that areas in the right hemisphere represent the slower rhythm stronger than homologues in the left hemisphere. Hemispheric separation of rhythms should lead to an increased information flow from the right to the left hemisphere when tapping slowly and from the left to right hemisphere when tapping fast. However, since the left hemisphere is dominant in motor planning, left to right information flow could be represented in both conditions and would be invisible in contrasts.
The bimanual symmetric conditions are of paticular interest, because in these conditions, different brain activation cannot be attributed to different effector use as in the unimanual conditions.

Different activation for internal and external timing
External timing is used to synchronize own movement with a sensory stimulus (auditory, tactile or visual) in the environment. If the stimulus shows a regular pattern, humans are able to anticipate and execute their movement in advance to the next stimulus (negative asynchrony (Repp, 2005; Repp and Su, 2013)). This predictive behavior is related to an enhanced activity in the dPMC (Kornysheva et al., 2011).
Internal timing is used when humans order their movement in a specific time range (e.g. in continuation tasks). This internal representation of given sequence tempo, requires working memory loops in the brain including the SMA. Monkeys in which the SMA was removed, "were impaired when they had to perform the movements at their own pace, but much less impaired when a tone paced performance" (Thaler et al., 1995). In both cases also subcortical structures like the cerebellum and the basal ganglia are involved.

The second contrast of interest is the one between the multifrequent conditions. We assume that one condition would be optimal by respecting the hemispheric preferences for relative frequencies (fast rhythm is tapped by the right hand) while the other condition would be non-optimal, violating the hemispheric preferences (fast rhythm is tapped by the left hand). While in the optimal condition information for performing the fast or slow movement is already in the executing hemisphere, in the non-optimal condition information has to cross the hemispheres via the corpus callosum. This should lead to an increased activation of hierarchically higher cortical loops, including frontal and parietal regions. Since we assumed that there will be more errors due to interference between the hemispheres (see section 1.1.1), we expected to find higher information transfer in the

non-optimal condition.

1.4 Structure of the thesis

We tested condition differences on the behavioral as well as on the neural level. This leads to a logic split in the following three chapters which are based on scientific publications. In a first behavioral experiment (chapter 2) we provide empirical evidence in the support of the DFF theory (Pflug et al., 2017).
In Chapter 3, we identify the neural mechanisms behind the differential rhythm representations in the two cerebral hemispheres (Pflug et al., 2019).
In chapter 4, MEG source signals were used to identify correlated EEG sensors. Those were selected for a combined EEG/fMRI analysis to investigate the relationship between BOLD signal and EEG beta oscillations Gompf et al. (2017). Additional results of neural differences between the syncopated and non-syncopated tapping paradigm will be mentioned in the discussion, but will be published later. Results of the second experiment, investigating fast and slow movements are currently processed but are not part of this thesis. The same holds true for the invasive recordings.

2 Bimanual tapping of a syncopated rhythm reveals hemispheric preferences for relative movement frequencies

Anja Pflug [a], Florian Gompf [a], and Christian Alexander Kell [a,*]

[a] Cognitive Neuroscience Group, Brain Imaging Center and Department of Neurology, Goethe University, Frankfurt, Germany

[*] Corresponding author. Tel.: +49-69-6301-6395; E-mail address: c.kell@em.uni-frankfurt.de

Acknowledgements

This study was supported by a LOEWE grant from the Land of Hesse to CAK. We are thankful to Johannes Kasper and Timo Fischinger for sharing their musical expertise as well as Marion Behrens and Benjamin Peters for statistical help, as well as Madeline Klinger for proofreading.

2.1 Abstract

In bimanual multifrequency tapping, right-handers commonly use the right hand to tap the relatively higher rate and the left hand to tap the relatively lower rate. This could be due to hemispheric specializations for the processing of relative frequencies. An extension of the double-filtering-by-frequency theory to motor control proposes a left hemispheric specialization for the control of relatively high and a right hemispheric specialization for the control of relatively low tapping rates. We investigated timing variability and rhythmic accentuation in right handers tapping mono- and multifrequent bimanual rhythms to test the predictions of the double-filtering-by-frequency theory. Yet, hemispheric specializations for the processing of relative tapping rates could be masked by a left hemispheric dominance for the control of known sequences. Tapping

was thus either performed in an overlearned quadruple meter (tap of the slow rhythm on the first auditory beat) or in a syncopated quadruple meter (tap of the slow rhythm on the fourth auditory beat). Independent of syncopation, the right hand outperformed the left hand in timing accuracy for fast tapping. A left hand timing benefit for slow tapping rates as predicted by the double-filtering-by-frequency theory was only found in the syncopated tapping group. This suggests a right hemisphere preference for the control of slow tapping rates when rhythms are not overlearned. Error rates indicate that overlearned rhythms represent hierarchically structured meters that are controlled by a single timer that could potentially reside in the left hemisphere.

Highlights

- The right hand taps relatively high rates more precisely than the left hand
- Syncopation unmasks a left hand benefit for slow tapping rates
- Frequency-dependent lateralization of relatively slow and fast timers occurs only when tapping unknown meters
- Tapping a standard meter may rely on integrated timing by a single timer in the left hemisphere

Keywords

Auditory-motor synchronization; Hemispheric specialization; Functional lateralization; Internal timing; Finger tapping

2.2 Introduction

When a right-handed person is asked to tap with one hand to every beat of an auditory stream and with the other hand to every second, third, or fourth beat, he or she will intuitively choose the right hand for tapping to every beat. In those multifrequent auditory-motor tapping paradigms, this represents the relatively high tapping rate. Right hand preference for fast tapping is expressed in a more accurate timing compared to the opposite hand arrangement where the left hand is tapping quickly (Peters and Schwartz, 1989). Studies on the observed asymmetry focus mainly on the role of the left hemisphere. Proposals for the origin of this functional asymmetry range from a dominance for motor control in general, to a specialization for sequencing, to preferred processing of relatively high frequencies by the left half of the brain.

A general left hemispheric dominance for motor control implies that the left hemisphere plans and integrates all movements independent of sequencing, movement speed, or effector (Fujiyama et al., 2016; Serrien et al., 2003; Jaencke et al., 2000a). Effector-independence was demonstrated in stroke patients with damage to left frontoparietal cortices that caused bilateral motor deficits. In contrast, right hemisphere lesions produced primarily only contralateral paralysis (Haaland, 2000; Haaland and Yeo, 1989). In consequence, the left hemisphere is thought to host internally stored effector-independent action representations (Leiguarda and Marsden, 2000; Mars et al., 2007). Which functional property grants the left hemisphere advantage over the right hemisphere in acquiring such "motor plans" is still a question of debate. Early studies of apraxia (Liepmann, 1905) and more recent observations suggest that the left hemisphere efficiently reproduces learned sequences (Dovern et al., 2016; Mars et al., 2007; Serrien and Sovijrvi-Spap, 2015).

Other theories of hemispheric dominance in motor control, like the

double-filtering-by-frequency theory (DFF), take both hemispheres into account. This has been first proposed in the sensory domain, but has lately been extended to motor control (Robertson and Ivry, 2000; Aboitiz and Montiel, 2003). The original version of the theory proposes that the two cerebral hemispheres differ in how they process relative stimulus frequencies of complex sensory input. While the left hemisphere is thought to preferentially process higher relative frequencies or local stimulus features, the right hemisphere excels in processing lower relative frequencies or global stimulus features (Ivry and Robertson, 1998; Flevaris and Robertson, 2016). If the hemispheres differ in how they process sensory information and this preference is represented in the underlying neural network structure (Galuske et al., 2000), then sensory-motor processing could benefit from representing the motor-related computations accordingly. Communication inside one hemisphere is faster than inter-hemispheric transfer across the corpus callosum, which has been associated with increased conduction times (Ringo et al., 1994). Consequently, the motor system could be organized with a left hemisphere preference for relatively faster and right hemisphere preference for relatively slower actions - eliciting faster, respectively slower sensory feedback signals.

Hemispheric preferences should not necessarily have consequences for unimanual or bimanual mono-frequency tapping. One hemisphere (typically the left) could control the timing for both hands via inter-hemispheric interactions (Serrien et al., 2003), yet with increased conduction times for ipsilateral hand control. Particularly, multifrequency tapping may reveal hemispheric specialization when the hemispheres are forced to control different tapping rates. The two aforementioned hypotheses (left hemispheric dominance versus DFF) propose different predictions for this condition. The tapping rates could be integrated in a common rhythmic frame in one hemi-

sphere with more precise timing of the contralateral hand. Alternatively, tapping rates could be segregated in the two hemispheres. In the latter case, the hemispheric preferences for relatively high vs. relatively low frequencies may translate into an optimal multifrequency tapping condition in which the right hand taps quickly and the left hand slowly. Neural control of such multifrequency tapping would thus rely on segregated processing.

Integration vs. segregation of neural control of tapping rates should depend on experience with the tapped metric structure (Drake and Palmer, 1993). Meter is accentuated rhythm that groups elements in sequences. Since multifrequency movement patterns are abundant - for example in moving to music - it is likely that often used metric patterns represent learned sequences. Therefore, their timing may be controlled by the left hemisphere (Kimura, 1993). A popular rhythm in Western culture is the quadruple meter (common time). In this meter, the first (and the third) beat of a sequence of four are accentuated while the second and fourth beats are un-accentuated (London, 2012). Due to cultural imprinting, tapping to the first beat of a quadruple meter represents a highly internalized rhythm in Western societies. When tapping this familiar multifrequency rhythm with both hands, timing of the two tapping rates may be hierarchically integrated into one sequence. According to the hypothesis of a general left hemispheric dominance, this integration would be controlled by the left hemisphere. Studies investigating multifrequency movements could not report a significant left hand benefit for tapping the relatively slower rates (Haaland and Harrington, 1994; Peters, 1985), a finding that could be expected based on the DFF theory. Integration of both tapping rates in a hierarchical rhythmic structure could potentially explain these negative findings.

However, when learning new bimanual sequences, communication

between the hemispheres is enhanced (Gerloff and Andres, 2002; de Guise et al., 1999). This is arguing for an active contribution of the right hemisphere in motor control under such circumstances (Andres et al., 1999; Karpati et al., 2016). In music, unintuitive rhythms are created when accents occur on otherwise un-accentuated beats (Cooper and Meyer, 1963). This syncopation of rhythm leads to a higher complexity – a strategy often used in classical and jazz music (Fitch and Rosenfeld, 2007). Our assumption is that in syncopated rhythms, fast and slow tapping rates are not (yet) integrated into one sequence but are rather represented separately in each hemisphere.

In a bimanual auditory paced finger tapping task, we investigated differences in timing accuracy and beat accentuation between tapping a standard quadruple meter (1-0-0-0 with 1 = tapping; 0 = pause) and tapping a syncopated quadruple meter (0-0-0-1). The two different meters were studied in different groups to avoid contextual interference effects (Ruitenberg et al., 2015; Young et al., 1993). Participants performed four bimanual tapping conditions. Two mono-frequency conditions were included (fast tapping (1-1-1-1) and slow tapping (1-0-0-0 in unsyncopated tapping) or (0-0-0-1 in syncopated tapping)) to test for tapping rate effects as proposed by the DFF theory (Robertson and Ivry, 2000). Two multifrequency conditions in which one hand taps the fast and one hand taps the slow tapping rate were investigated. According to the hypothesized hemispheric preferences in right-handed people, an optimal hand arrangement is represented by the right hand tapping the fast and the left hand the slow rate. For the non-optimal hand arrangement, tapping rates are switched, with the left hand tapping the fast rate. Inter-tap-interval deviation is a measurement for timing accuracy. Standard deviation of absolute deviation represents timing stability independent of direction of inaccuracy. This variable was used

to evaluate how timing processes are affected by either syncopation or condition. Tapping pressure was recorded to investigate tap accentuation within sequences. Accentuation patterns can be used to reveal rhythmic grouping, which is easier for less complex rhythms (Mattheson, 1739; Dowling, 2014).

In case of a general left dominant motor control, the right hand should tap more precisely independent of tapping rate, condition, or syncopation since inter-hemispheric conduction delays disadvantage the left hand. A conservative interpretation of the DFF theory would predict each hemisphere to be optimized for its relative tapping rate independent of the degree of internalization of motor sequences. In this case, preferences of the right hand for tapping the fast rate and of the left hand tapping the slow rate should be found independent of syncopation. A third possibility takes both frequency dependency and internalization into account. If the left hemisphere controls over-learned rhythms independent of the effector, a right hand benefit for both tapping rates and all conditions should be observed only in the unsyncopated tapping group (standard meter). If syncopation leads to segregation of tapping rates, the control of these rates could be represented separately on the two hemispheres. The DFF theory proposes a left hemispheric preference for fast tapping rates and a right hemispheric preference for slow tapping rates. As a consequence, an optimal hand arrangement reflecting these preferences (left hand slow, right hand fast) should lead to a higher precision for both hands than the opposite arrangement.

2.3 Material and Methods

2.3.1 Participants

Twenty participants (eight male, 21-38 years, mean 27.2 years) were included in this study. Three participants had professional musical training and six actively played an instrument (3 of them less than once a month). Participants had no neurological deficits and were right-handed according to self report and their scores on the Edinburg inventory of manual preference (mean handedness quotient 91.25, range 65-100; Oldfield 1971). Participants were randomly split into two groups. Five participants were included in both experiments with a minimum of three days in between the measurements. In each experiment, four participants played an instrument more often than once a month (of these two professionals participated in the unsyncopated group and three professionals in syncopated tapping group). All participants gave their written informed consent prior to the experiment and were paid for their participation. The study was approved by the local ethics committee and is in accordance with the declaration of Helsinki.

2.3.2 Methods

2.3.2.1 Experimental setup

Participants sat in front of a computer monitor on which the visual instruction was presented. Participants' gaze was not restricted. Two pneumatic Biopac pressure sensors (module of model MP150, BIOPAC Systems, INc., Goleta, CA, e.g. see Dong et al. 2012) were fixed on the table in front of them. The pressure sensitivity was 0.01 cm H_2O with a sampling rate of 1 kHz. Auditory beats (1600 Hz, 2 ms) were presented with a constant inter-onset-interval of 400 ms (2.5 Hz, 210 bpm) via headphones. Pacing signal and visual instructions were presented with Presentation software (Neu-

robehavioral Systems, Albany, CA, USA).

2.3.2.2 Unsyncopated tapping

In the first group, twelve participants were asked to tap bimanually with their index fingers in two different rates synchronized to the auditory beats. A fast tapping rate was defined as tapping to every auditory beat. For slow tapping rates, participants were instructed to iteratively count four beats internally and tap only on beat position one (equivalent to a quarter note followed by a three quarter rest 1-0-0-0). Participants were instructed to either tap the same rate with both hands (monofrequency: both fast (FF) or both slow (SS)) or to produce two different tapping rates (multifrequency) in which one hand taps the fast and the other one taps the slow rate (see Figure 2.1). Multifrequency tapping was either performed in the optimal hand arrangement, where the right hand taps the fast and the left hand the slow rate (SF), or in the opposite non-optimal hand arrangement (FS). The task was performed in three runs with 12 trials each, in semi-randomized order (within each run). In total, every condition was performed nine times.

A trial started with a 2.5 – 4 s presentation of a visual instruction (upward arrows for fast, downward arrows for slow conditions) that indicated which upcoming condition had to be performed. Before participants started tapping, four auditory beats of higher pitch primed the rate. 36 auditory beats were presented in 15 seconds, resulting in 36 taps in fast and nine taps in slow conditions. The inter-block interval was jittered in both recordings to reduce temporal predictability.

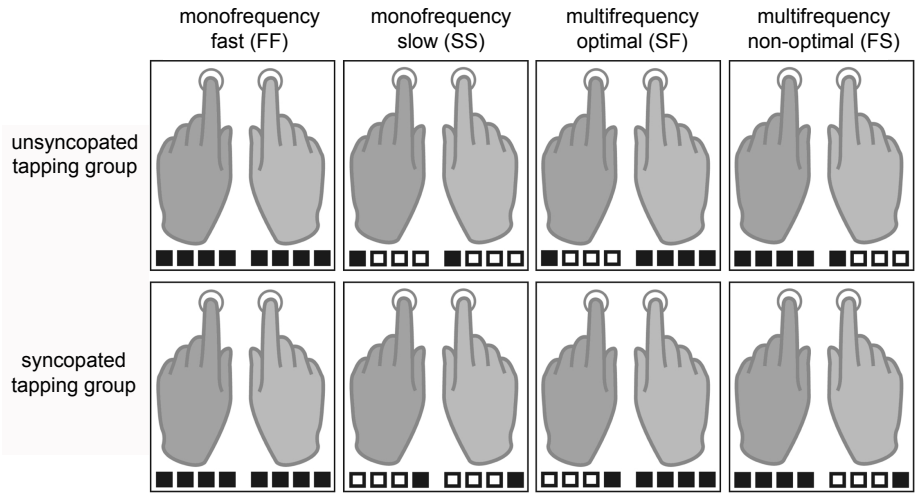

Figure 2.1: Tapping conditions. Filled squares represent tapping events, white squares represent auditory beats without tapping in slow tapping rates. Participants were instructed to tap to the first position of four consequent auditory beats in the unsyncopated tapping paradigm and to the fourth position in the syncopated tapping paradigm.

2.3.2.3 Syncopated tapping

In the other group, thirteen participants were also asked to tap at two different rates. The fast tapping rate was the same as that of the unsyncopated tapping group, while for the slow tapping rate, participants tapped on the fourth instead of the first beat of a sequence of four (0-0-0-1). Like in the unsyncopated tapping paradigm, participants tapped four different conditions (FF, SS, SF, FS).

2.3.3 Data Analysis

The maximal pressure of each tap was used as a reference point for temporal analysis. Trial data of both hands were visually inspected and those in which participants failed to follow the instructions or rested their fingers on the pad before tapping were dismissed (in total FF=11, SS=14, SF=10, FS=11). Taps were detected semi-automatically (manual threshold adaptation) with an in-house cre-

ated algorithm in Matlab (MATLAB and Statistics Toolbox Release 2012b, The MathWorks, Inc., Natick, MA, USA). Taps were numbered with position relative to beat sequence (1:36) and renumbered in sequences of four (1,2,3,4,1,...). Taps with a temporal distance larger than ± 200 ms from the equivalent beat were treated as outliers and eliminated. Sequences of four consecutive beats were visually inspected using Fieldtrip (Oostenveld et al., 2011). In fast tapping conditions, four consecutive taps were defined as a valid sequence. Sequences in slow tapping conditions were only valid if they included only one tap at the intended position (unsyncopated group - first auditory beat, syncopated group - fourth auditory beat). In six participants of the syncopated and four participants of the unsyncopated tapping group, errors occurred in the slow tapping rate of the multifrequency conditions. These sequences (1.7 % of multifrequency sequences) were eliminated from further analysis of timing variability and pressure. Their distribution over conditions and groups was further examined (see Statistical analysis section). The first sequence of each trial was not included in the analysis, because it was prone to errors. Thus, trials consisted of tapping data for eight sequences in total. For both tapping rates, two dependent variables were calculated separately for each condition, hand, and participant: timing variability and pressure. While the first represents a measure of variability in timing, the second is a measure of accentuation and therefore could indicate processing of rhythmic structure (Dowling, 2014). Timing variability was calculated using the standard deviation of absolute distance between the actual inter-tap-intervals and the target inter-tap-interval (400 ms for fast, 1600 ms for slow tapping rates) of consecutive taps. Since not every participant tapped with the same intensity, pressure amplitude values were normalized to the participant's mean independent of hand and tapping rate (values * 100/mean (values)), resulting in percentage

values compared to the participant's mean pressure.

2.3.4 Statistical Analysis

We analyzed taps associated with slow and fast tapping rates separately, also because there were four times more taps associated with the fast tapping rate than taps associated with the slow tapping rate. Since values of timing variability were not normally distributed, a logarithmic transformation was performed, but for reasons of clarity, original values are illustrated. Transformed values were used as dependent variables for both tapping rates in a 2 (group [unsyncopated, syncopated]) x 2 (hands [left, right]) x 2 (condition [monofrequent, multifrequent]) mixed design repeated measure analysis.
The same analysis was performed for pressure of taps associated with the slow tapping rate. To analyze pressure of taps associated with the fast tapping rate, a 2x2x2x4 mixed design repeated measure analysis of variance was performed with factors group, hand, condition, and beat-number [1,2,3,4]. Pressure data were normally distributed. Thus, no transformation was needed.
Significant effects were post-hoc tested using paired-sample t-tests for effects within the groups and two-sample t-tests for between group effects. Significance level (alpha) was set at 0.05, effects between 0.05 and 0.075 were discussed as tendencies. Repeating all ANOVAs with the exclusion of musical professionals did not significantly change the results (all significant effects remained significant and all trends remained trends).
A post hoc test was performed to further investigate an observed inverse effect of condition on timing variability as a function of tapping rate. This was done by subtracting mean values (over both hands) of the multifrequent conditions from mean values of the monofrequent condition for both tapping rates separately. These differences were tested for Pearson's correlation ($\mathbf{p} < 0.05$).

Distributions of error sequences over conditions and groups were analyzed using a Chi-square test. Statistical tests were conducted using SPSS Statistics 22.0 (IBM Company) and Matlab (MATLAB and Statistics Toolbox Release 2012b, The MathWorks, Inc., Natick, Massachusetts, United States).

2.4 Results

2.4.1 Timing variability

2.4.1.1 Fast tapping rate

Significant main effects of hand ($F(1,24) = 15.34$, $p = 0.001$) and condition ($F(1,24) = 30.87$, $p < 0.001$) were found. Fast tapping was more precise when performed by the right compared to the left hand independent of syncopation and condition (Figure 2.2a). Multifrequency tapping led to an increase in variability compared to monofrequency FF (solid line, Figure 2.3).

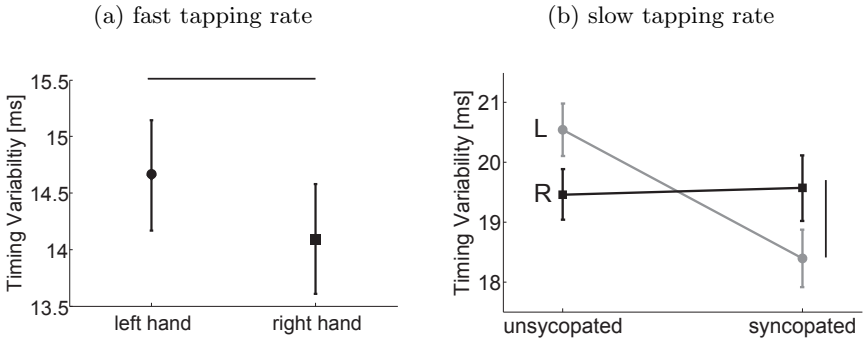

Figure 2.2: Timing variability. Smaller values represent better performance. Black lines indicate significant differences ($p < 0.05$). Error bars represent the standard error of the mean. Panel a shows timing variability of fast tapping as a function of effector. Panel b shows the interaction between hand and group for taps associated with the slow tapping rate (gray = left hand (L), black = right hand (R)).

2.4.1.2 Slow tapping rate

Taps in multifrequency conditions were timed more precisely compared to monofrequency SS (main effect of condition $F(1,24) = 33.00$ $p < 0.001$, see dashed line Figure 2.3). There was no significant correlation between the timing benefit in slow tapping and the performance decrease in fast tapping ($r = 0.23$, $p = 0.27$) in the multifrequency conditions. No main effect of hand, but a non-significant tendency towards an interaction between hand and group was found ($F(1,24) = 4.05$, $p = 0.056$). Post-hoc testing revealed that only in the syncopated tapping group, left hand was higher than right hand tapping accuracy ($t(12) = 2.23$, $p = 0.046$, Figure 2.2b). In the unsyncopated tapping group, no difference in performance between hands was found ($t(11) = 0.094$, $p = 0.517$, Figure 2.2b). Testing the differences between groups for left, respectively right hand performance with two-sample t-tests did not reveal significant effects.

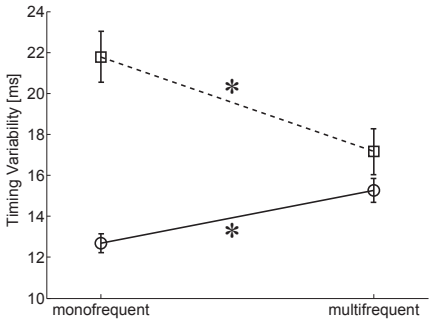

Figure 2.3: Timing variability as a function of tapping condition (monofrequent and multifrequent) for slow (squares) and fast (circles) tapping rates. Smaller values represent better performance. Asterisks indicate significant differences ($p < 0.05$). Error bars represent the standard error of the mean.

2.4.2 Pressure

2.4.2.1 Fast tapping rate

A main effect of beat number ($F(3,72) = 12.85$, $p < 0.001$), an interaction between beat number and group ($F(3,72) = 10.29$, $p < 0.001$), and a triple interaction between beat number, group, and condition ($F(3,72) = 8.90$, $p < 0.001$) confirmed that the two groups accentuated different beat numbers depending on the performed meter. The unsyncopated tapping group accentuated beat number one expectedly (Figure 2.4a). In the syncopated tapping group, accentuation of beat number one was conserved in addition to an expected accentuation of beat number four (Figure 2.4b). Note that monofrequency fast tapping did not show effects of beat position, as expected (dashed lines in Figure 2.4a and b).
In both groups, multifrequency tapping lead to a higher pressure than monofrequent tapping (main effect of condition $F(1,24) = 7.05$, $p = 0.014$), although this effect was mainly driven by the syncopated tapping group (see Figure 2.4b). Overall, pressure in taps associated with the fast tapping rate was stronger in the unsyncopated compared to the syncopated tapping group (main effect of group $F(1,24) = 10.62$, $p = 0.003$).

A triple interaction between beat number, hand, and group ($F(3,72) = 3.90$, $p = 0.022$) and a tendency for a triple interaction between beat number, hand, and condition ($F(3,72) = 2.91$, $p = 0.057$), and a quadruple interaction between hand, condition, group, and beat number ($F(3,72) = 5.47$, $p = 0.005$) was explained by an effect in multifrequent conditions only in the syncopated tapping group. Post hoc testing in this group revealed a pressure increase between beat number three and four in both multifrequent conditions (SF $t(12) = 2.57$, $p = 0.025$ and FS $t(12) = 3.913$, $p = 0.002$). When comparing this increase between the conditions, it was higher in FS

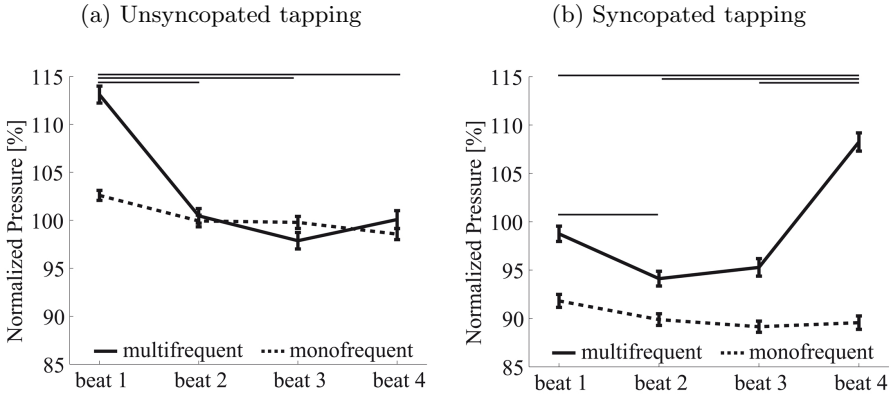

Figure 2.4: Normalized pressure as a function of beat position associated with the fast tapping rate for both groups. Dashed line monofrequency tapping (FF); solid line multifrequency tapping mean of both hands. Black lines indicate significant differences ($p < 0.05$). Error bars represent the standard error of the mean. Panel a shows accentuation in the unsyncopated tapping group. Panel b shows accentuation in the syncopated tapping group.

than in SF ($t(12) = 2.41$, $p = 0.033$, Figure **??**.

2.4.2.2 Slow tapping rate

In both groups, taps associated with the slow tapping rate (M = mean, SD = standard deviation; $M = 114.03$, $SD = 15.83$) were more strongly accentuated than taps associated with the fast tapping rate ($M = 98.28$, $SD = 6.38$; $t(22) = 4.21$, $p < 0.001$, not illustrated). Slow taps in multifrequent conditions ($M = 102.37$, $SD = 12.85$) were less strongly accentuated compared to slow taps in the monofrequent condition SS ($M = 104.42$, $SD = 17.38$; main effect of condition $F(1,24) = 8.34$, $p = 0.008$, not illustrated).

2.4.3 Tapping errors

In some multifrequency sequences, participants not only tapped on the intended beat position (one in unsyncopated and four in syncopated tapping) but also on the following beat position (two in un-

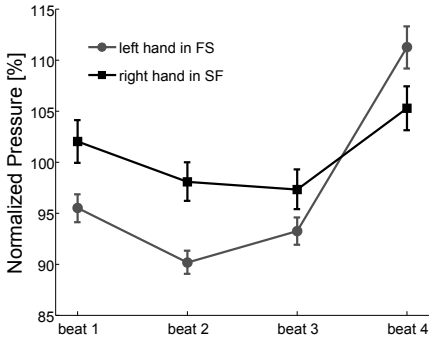

Figure 2.5: Normalized pressure as a function of beat number for taps associated with the fast tapping rate in multifrequency conditions of the syncopated tapping group (right hand (squares) and left hand (circles)). Error bars represent the standard error of the mean.

syncopated, one in syncopated). Sequences in multifrequency conditions with more than one tap per sequence were defined as errors. By definition, these errors reflected incorrect slow tapping. A chi-square test of independence was performed to examine the percentage distribution of error sequences between the two multifrequency conditions. The non-optimal hand arrangement (FS) showed expectedly more errors than the optimal hand arrangement (SF)($X^2(1) = 4.38$, $p = 0.036$, see Table 2.1). This effect was stronger in the syncopated tapping group (difference of 33.4%) than in the unsyncopated tapping group (difference of 6.6 %). In the unsyncopated tapping group, errors were more equally distributed between the two multifrequent conditions (see Table 2.1).

	optimal	**non-optimal**	**number of errors**
unsyncopated	16.7 %	23.3 %	12 (5|7)
syncopated	13.3 %	46.7 %	18 (4|14)

Table 2.1: Percentage distribution and numbers of errors occured in the two tapping groups. Values in brackets indicate numbers of error sequences in optimal|non-optimal conditions.

2.5 Discussion

2.5.1 Syncopation unmasks a right hemisphere preference for slow tapping rates

A right hand benefit for tapping quickly in multifrequency tapping paradigms is predicted by both a general left hemisphere dominance for motor control theories as well and the DFF theory. Indeed, fast tapping was less variable when performed by the right hand. This suggests a left hemispheric preference for controlling fast tapping rates. However, the hypotheses diverge regarding their predictions for slow tapping performance. While a general left hemisphere dominance for motor control would result in a rate-independent superiority of the right hand, the DFF theory would predict a better performance of the left hand over the right hand when tapping slowly. Neither scenario was found.

The hand x group interaction can only be explained by a third proposal assuming processing of integrated sequences in a single hemisphere and right- and left-lateralized processing of relative frequencies for new sequences. The left hand benefit for slow tapping in the syncopated tapping group suggests a right hemispheric timer for relatively low frequencies. Syncopation unmasks this right hemispheric preference for slow tapping rates which may otherwise be overlaid by a left hemisphere dominance for the control of known rhythms. We expected to reveal possible hemispheric preferences especially in multifrequency conditions, in which movements for fast and slow rates were produced by different hemispheres. Yet, the left hand benefit for tapping the slow rate in the syncopated tapping group was also found in the monofrequency condition in which both hands tapped the slow rate (no triple interaction). Note that slow monofrequency, syncopated tapping represents a non-overlearned rhythm. Even in the monofrequency slow tapping condition, both slow and fast rhythms were processed by the participants because the audi-

tory beats correspond to the fast rhythm. This suggests an internal meter representation that for syncopated tapping may likely involve both hemispheres. Since slow and fast rhythms are consequently processed in parallel, their relationship is crucial in all conditions except FF, as proposed by the DFF theory. Note that our study design does not allow dissociating absolute from relative frequencies, yet empirical observations strongly suggest that relative rather than absolute frequencies are associated with functional lateralization (Ivry and Robertson, 1998). The observed left hand benefit implies that the right hemisphere generates the slow rhythm in the context of a relatively faster rhythm as long as it is not yet overlearned. This implies that an internal timer with a preferred lower frequency in the right compared to the left hemisphere is used for all non-overlearned conditions in which the left hand taps slowly, independent of the right hand's performance. Such a finding strongly argues against a left hemispheric dominance for motor control in general. It rather specifies the frequency dependent lateralization proposed by the DFF theory only for non-overlearned rhythms.

The left hand preference for slow tapping was not observed in the group tapping the standard quadruple meter. This metrical structure is overlearned in Western civilization and could potentially be represented in the form of an integrated Gestalt. In music *perception*, musical beats of different temporal frequencies are integrated in a higher metrical structure and perceived in one perceptual stream (Bregman, 1994). Proficiency in perception of rhythmic structure indeed leads to the integration of different beats in an auditory Gestalt and to the lateralization of auditory processing to the left hemisphere (Vuust et al., 2005). In contrast, when non-professionals listen to a syncopated rhythm, they often report a perceptual stream segregation (Fitch and Rosenfeld, 2007). This is in line with a more individual representation of beat and me-

ter (Nozaradan et al., 2012). Previous behavioral data (Keller and Burnham, 2005) and our results suggest that the *production* of multifrequency structures is also based on integrated rhythms. This is suggestive of acquired neural representations of such hierarchical structures, potentially in the left hemisphere (Kimura, 1993). Of note, auditory stimulation was constant in our experiment. Consequently, complex auditory input is not necessary to elicit these hemispheric differences in rhythm processing. Internal timing may equally use neural infrastructure otherwise used for rhythm perception (Chen et al., 2006; Merchant and Honing, 2014). This study did not systematically investigate musicians, who should perform better in integrating complex rhythms. It can be speculated that the initial segregation of relative timers in the hemispheres occurs during a much shorter learning phase compared to non-musicians up until the left hemisphere integrates these rhythms hierarchically. Rhythm integration may rely upon cross-frequency coupling in cortical hierarchies, a neural mechanism that is left-lateralized during speech processing (Gross et al., 2013).

2.5.2 Metric structure in fast tap pressure

Monofrequency fast tapping represents simple synchronization to the auditory beat as evidenced by the lack of tap position effects on pressure in this condition. The observed increase in pressure for multi- compared to monofrequency tapping could be interpreted as additional representation of the fast rate in the context of a second (slower) tapping rate. In the syncopated tapping group, starting to count at beat position one was aligned with higher pressure, even if participants were instructed to tap on the fourth beat. This underlines the importance of the first beat for defining a sequence (Povel and Essens, 1985; Rhodes et al., 2004; Verwey, 1999). The stronger accentuation of the left compared to the right hand on tap

number four in the non-optimal condition in the syncopated tapping group complements the timing variability findings that suggest a right hemisphere timer for lower relative frequencies. Increased pressure on beat number four of the fast tapping hand may reflect a stronger representation of the meter.

2.5.3 Violation of hemispheric preferences increases number of errors

The fact that tapping errors were equally distributed between the two multifrequency conditions in the unsyncopated tapping group speaks in favor of an integration of the two tapping rates into one metrical structure. Given the lower error rate in the unsyncopated tapping group, an integration of rhythms which could potentially be controlled by a single hemisphere seems to be beneficial for performance. In contrast, syncopation increased tapping errors when hemisphere preferences for the processing of relative frequencies were violated. This confirms better control in the optimal compared to the non-optimal condition. Whether this represents a consequence of superior intra- or interhemispheric interactions remains to be determined by neurophysiological experiments.

2.5.4 Overt subdivision benefit

It is known that longer intervals show a higher variability in timing. This can be by using auditory stimuli in between the taps, a phenomenon termed subdivision benefit (Repp, 2003). In multifrequency conditions, internal timing was more precise for taps associated with the slow tapping rate. Such an effect is called an overt subdivision benefit (Repp, 2010) and has been demonstrated already for 2:1 tapping (Semjen and Summers, 2002). Fast "intertaps" may represent a more precise reference for central timekeeping processes than auditory input alone, potentially due to the additional somatosensory input. While this effect seems to be ben-

eficial for tapping slowly, the fast intertaps are timed less precisely compared to monofrequency fast tapping. The lack of correlation between variability decrease for slow tapping and variability increase for fast tapping suggests that the improvement in tapping the slow rate did not occur directly at the expense of fast tapping rate acuity. Pressure of taps associated with both – the slow and the fast – tapping rate followed the aforementioned pattern for timing variability. It is still a question of debate if timing and pressure depend on different or identical neural sources.

2.5.5 Limitations

2.5.5.1 Neural origin

We hypothesized that the observed manual preferences have a hemispheric, neocortical origin. However, timing has mainly been associated with the cerebellum and defined intervals may activate cerebellar columns with temporal tuning (Ivry and Richardson, 2002). Our results may therefore also be explained by a different composition of time columns in the left and right cerebellum contralateral to the neocortical hemispheres and ipsilateral to the tapping hand. Yet, the neocortex together with the basal ganglia, thalamus, and the cerebellum form functional networks that jointly serve timing processes. We believe that future research is unlikely to reveal a single origin of functional lateralization, but will rather identify the different contributions of subcortical and cortical processes.

2.5.5.2 Left-handedness

We only tested right-handed participants. We do not claim that our findings generalize to left-handers. They may either show an inverse pattern of organization or reduced cerebral asymmetries. Empirical findings suggest that the latter is the case. The lateralization strength seems to be weaker in left handed people (Serrien et al.,

2012). While most right-handers generally show a strong asymmetry between the hands for fast tapping, this asymmetry is reduced in left-handers (Peters and Durding, 1979; Mellet et al., 2014) . When people tap with one hand as quickly as possible while the other hand follows a slower beat, right-handers perform significantly better with their optimal combination (left hand following the beat, right hand maximal speed) while left-handers showed no clear superiority of one hand. Their performance for both combinations was in between the optimal and non-optimal hand arrangement of right handers (Peters, 1987). Altogether, previous reports suggest diminished lateralization in left-handers.

2.5.5.3 Alternative theories

The DFF theory is not the only theory that proposes a specific feature that underlies the origin of hemispheric asymmetries for manual hand preferences. An alternative framework is the dynamic dominance hypothesis (Sainburg, 2002). This framework proposes that the left hemisphere is optimized for dynamic control and the right hemisphere is optimized for positional control of movements. While this theory can be used to explain asymmetries in static and dynamic movements, it cannot explain preferences in multifrequency tapping paradigms, in which only the rate of events is manipulated. Thus, there may be more than one factor contributing to hemispheric specialization, relative frequencies being only one of them.

2.6 Conclusion

We tested two influential theoretical proposals for hemisphere specialization in controlling finger tapping. Although we only analyzed behavioral data, our results hint at processing differences between the hemispheres. A functional lateralization of low relative frequencies to the right hemisphere, as proposed by the DFF theory, was

only found when the produced rhythms were not yet overlearned. A possible interpretation could be that neural resources for tapping control were segregated between hemispheres leading to a lateralization of timers with different relative processing frequencies: a timer with faster oscillations in the left and a timer with slower oscillations in the right hemisphere. On the other hand, known sequences, even if they involve different frequencies, seem to be controlled by a single timer which could likely reside in the left hemisphere. Potentially, this could result from a left hemisphere dominance in processing hierarchically organized rhythmic structures. Our data are suggestive of the aforementioned relationships between tapping rates and hemispheric control. Neuroimaging and electrophysiological experiments are required to determine the neural structures that form the proposed frequency-dependent timers.

3 Differential contributions of the two human cerebral hemispheres to action timing

Anja Pflug [a,+], Florian Gompf [a,+], Muthuraman Muthuraman [b], Sergiu Groppa [b], and Christian Alexander Kell [a,*]

[a] Cognitive Neuroscience Group, Brain Imaging Center and Department of Neurology, Goethe University, Frankfurt, Germany

[b] Movement Disorders and Neurostimulation, Biomedical Statistics and Multimodal Signal Processing Unit, Department of Neurology, Johannes Gutenberg University, Mainz, Germany

[+] These authors contributed equally to this work

[*] Corresponding author. Tel.: +49-69-6301-6395; E-mail address: c.kell@em.uni-frankfurt.de

Acknowledgements

This study was funded by the German Research Foundation with an Emmy Noether Grant to CAK (KE 1514/2-1) and by a LOEWE grant of the state of Hesse (NEFF). We are thankful to Alla Brodski and Georg Friedrich Paatsch for assisting the MEG measurements.

3.1 Abstract

Rhythmic actions benefit from synchronization with external events. Auditory-paced finger tapping studies indicate the two cerebral hemispheres preferentially control different rhythms. It is unclear whether left-lateralized processing of faster rhythms and right-lateralized processing of slower rhythms bases upon hemispheric timing differences that arise in the motor or sensory system or whether asymmetry results from lateralized sensorimotor interactions. We measured fMRI and MEG during symmetric finger tapping, in which fast tapping was defined as auditory-motor synchronization at 2.5 Hz. Slow tapping corresponded to tapping to every fourth auditory beat (0.625 Hz). We demonstrate that the left auditory cortex

preferentially represents the relative fast rhythm in an amplitude modulation of low beta oscillations while the right auditory cortex additionally represents the internally generated slower rhythm. We show coupling of auditory-motor beta oscillations supports building a metric structure. Our findings reveal a strong contribution of sensory cortices to hemispheric specialization in action control.

Keywords

Lateralization; Hand motor control; Auditory cortex; Internal Timing; Theta oscillations; Finger tapping; Beta partial directed coherence

3.2 Introduction

Functional asymmetries between the two hemispheres are an intriguing principle of brain organization. On the behavioral level, these become most evident in the way humans use their hands. In tasks requiring movements of both hands, right-handers typically use the right hand for the faster, dynamic movements while the left hand is used for slower movements, or even static control of hand position (Sainburg, 2002; Swinnen and Wenderoth, 2004; Serrien and Sovijrvi-Spap, 2015). Cutting bread or hammering a nail into the wall represent everyday examples for such functional asymmetries. In the lab, finger tapping can be used to detect hemispheric asymmetries related to this phenomenon. Typically, the right hand taps relative higher tapping frequencies more precisely than the left hand even in bimanual monofrequent finger tapping (Repp, 2005; Ivry, 1996; Peters, 1980). Conversely, the left hand taps relative lower tapping frequencies more precisely than the right hand (Pflug et al., 2017). This suggests the left hemisphere preferentially controls relative higher tapping frequencies and the right hemisphere preferentially controls relative lower tapping frequencies, but the

origins of such hemispheric asymmetries are not known.

There are several proposals on the origins of functional differences between the hemispheres ranging from specialized processing in the sensory domain, lateralized sensorimotor interactions, asymmetric motor control, to domain-general frameworks on hemispheric dominance (Kimura, 1993; Minagawa-Kawai et al., 2007; Toga and Thompson, 2003; Kell and Keller, 2016). Behavior could benefit from parallel processing of different aspects of complex stimuli and/or movement planning in the left and right hemisphere (Serrien et al., 2006). Influential theories suggest differential sensory processing of relative frequencies either in the spectral or the temporal domain (Ivry and Robertson, 1998; Flevaris and Robertson, 2016; Poeppel, 2003) as computational bases of hemispheric specialization. However, empirical studies in which spectral or temporal aspects of the sensory input were parameterized did not always support those theories (Luo et al., 2007; Giraud and Truy, 2002; Boemio et al., 2005). This could represent a consequence of the fact that brain activity is only subtly lateralized during perceptual tasks. However, functional lateralization is thought to be amplified once a motor output is required (Ivry and Robertson, 1998; Keller and Kell, 2016).

To dissociate the specific contributions of the sensory and motor systems to functional lateralization of hand control, we performed two imaging studies using functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG). The study design excluded that condition effects resulted from sensory stimulus features or differential effector use. In an auditory-paced finger tapping paradigm, participants were asked to tap bimanually to auditory beats. Tapping to every auditory beat (2.5 Hz) was defined as the fast tapping condition while tapping to every fourth auditory beat (beat position four) represented slow tapping at 0.625 Hz (see Figure 3.1).

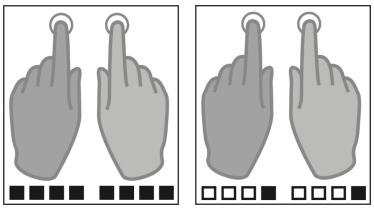

Figure 3.1: Tapping conditions. Participants were instructed to tap either to every beat (fast tapping, left panel) or to the fourth position of four consequent auditory beats (slow condition, right panel). Filled squares represent tapping events, white squares represent auditory beats without tapping in the slow tapping condition.

Both frequencies fall into the natural range of finger movements but represent different ends of the spectrum (Parncutt and Cohen, 1995; London, 2012; Drake and Palmer, 2000; Repp, 2003). While in the fast tapping condition, the fast auditory beat was the only rhythm that was processed and used for auditory-motor synchronization, this faster rhythm served as a timing signal to generate a slower rhythm in the slow tapping condition. The slow tapping condition was of primary interest in our study, because during slow tapping two interrelated rhythms had to be represented in parallel, a condition that could potentially reveal hemispheric specialization for controlling rhythms of different relative frequencies (Ivry and Robertson, 1998). A prior behavioral study (Pflug et al., 2017) suggested that representing a relative slow rhythm in parallel to a faster one should reveal the contribution of the right hemisphere to hand control. While we used fMRI to detect whether auditory or motor regions show a more pronounced lateralization profile, which answers the question of different contributions of the sensory and motor systems to hemispheric specialization, we used MEG to identify hemispheric differences in brain rhythms associated with finger tapping in a time-resolved manner and to investigate time resolved directed connectivity between auditory and motor association cor-

tices (Figure 3.2).

Movement is known to suppress beta oscillations and to increase activity in the gamma range (Muthuraman et al., 2012; Tamas et al., 2018; Pfurtscheller et al., 2003; Pfurtscheller and Lopes da Silva, 1999; Engel and Fries, 2010). Yet, neural oscillations, particularly in the beta range, not only reflect current motor state but are also implicated in internal timing, especially during rhythm processing, and are amplitude-modulated during rhythm perception and production not only in the motor and supplementary motor cortex, but also in the auditory and auditory association cortex (Arnal and Giraud, 2012; Doelling and Poeppel, 2015; Nobre et al., 2007; Fujioka et al., 2015; Meijer et al., 2016; Morillon et al., 2014; Kilavik et al., 2013; Kulashekhar et al., 2016; Morillon and Baillet, 2017; Iversen et al., 2009). Comparing neural oscillations during slow and fast rhythmic finger tapping may reveal the way the brain represents the two different rhythms in parallel. Amplitude modulations of beta oscillations should differ between functional homologues in case there were hemispheric processing differences in timing of relative tapping frequencies. We hypothesized that motor and/or auditory cortices may not only differ in overall beta power but also in terms of their degree of representing the slow and fast rhythms in the temporal modulation of beta power (Fujioka et al., 2015; Morillon and Baillet, 2017). If the predictions from the signal-driven hypotheses on hemispheric specialization (Ivry and Robertson, 1998) hold true, we specifically expected the right auditory cortex to more strongly represent the slow rhythm and the left auditory cortex the fast rhythm during slow finger tapping, the condition that comprised both rhythms. A left dominance in hand motor control based on left-lateralized sequencing skills (Kimura, 1993; Haaland et al., 2004), instead, would predict control of both rhythms by the left hemisphere.

Functional specialization of the two hemispheres has not only been

linked with lateralized regional activation, but also with the formation of lateralized functional networks of regions (Stephan et al., 2003; Keller and Kell, 2016). We thus investigated whether auditory-motor interactions between the right and left auditory association cortex and the supplementary motor area (SMA), a motor association area highly involved in the internal generation of sequences (Kotz et al., 2009; Merchant et al., 2013, 2015; Crowe et al., 2014), were modulated differently in the two hemispheres when representing the slow in addition to the fast rhythm. We hypothesized that auditory-motor effective connectivity may differ between the two hemispheres in terms of connection strength in the beta range.

Our results identify the left auditory association cortex as the primary cortical area that represents the relative fast auditory rhythm while the right auditory association cortex is recruited to represent the relative slow tapping rate in an amplitude modulation of low beta oscillations. In contrast, motor cortices and the cerebellum only represent the temporal regularities of the motor output. Representing the slow in addition to the fast rhythm increases low beta functional connectivity from the right auditory association cortex to the SMA in parallel to increased BOLD activation of these regions. Further, stronger and bidirectional low beta functional connectivity between the SMA and the left auditory association cortex may privilege the left hemisphere for hierarchical integration of interrelated rhythms in a Gestalt (Iversen et al., 2008; Swinnen and Wenderoth, 2004).

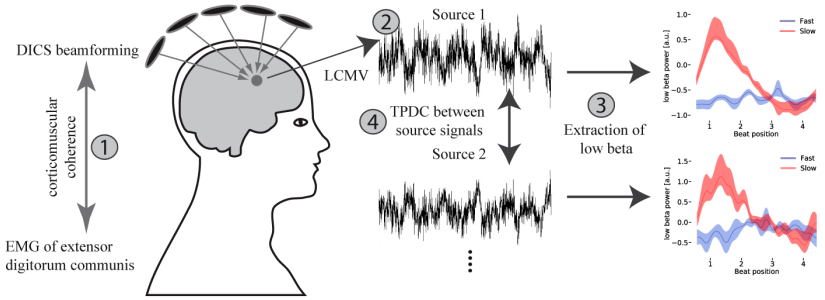

Figure 3.2: Overview of the applied MEG analysis steps: 1) Coherent sources with the EMG signal were detected at fast tapping frequency using a DICS beamformer 2) timeseries signals were extracted from the localized sources using an LCMV beamformer. 3) A sliding window time-frequency analysis was applied to transform these signals into a time-frequency-representation (TFR). By averaging over frequencies (14-20 Hz) a low beta band signal was extracted. 4) Source signals were fed into a time and frequency resolved directed connectivity analysis (TPDC).

3.3 Results

3.3.1 Performance measures indicate hemispheric specializations for relative frequencies

Timing variability was defined as standard deviation of the absolute distance between the actual and target inter-tap-intervals (Pflug et al., 2017). This measure characterizes internal timing well (Repp, 2005). A two-factor repeated measures analysis of variance (ANOVA) on timing variability across condition (slow and fast bimanual tapping) and hand (left and right) revealed expectedly an interaction between condition and hand ($F(1,41) = 10.23$, $p = 0.003$). Fast tapping was more precise with the right than the left hand (right hand: mean(M) = 13.29 ms, standard deviation (SD) = 2.74 ms; left hand: M = 14.41 ms, SD = 2.78 ms) and slow tapping was more precise with the left compared to the right hand (right hand: M = 33.78 ms, SD = 18.42 ms; left hand: M = 31.70 ms, SD = 14.97 ms, see Figure 3.3).

No main effect of hand was observed ($F(1,41) = 0.760$, $p = 0.388$).

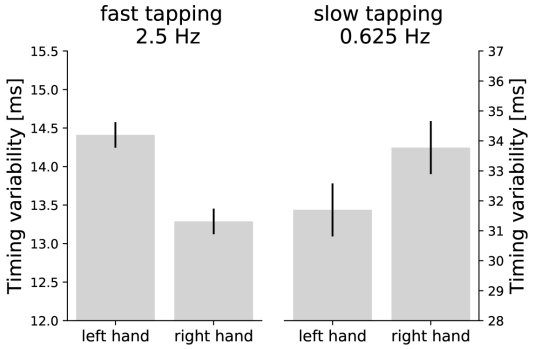

Figure 3.3: Asymmetries in performance. Timing variability is defined as standard deviation of the absolute distance between the actual and target inter-tap-intervals (Pflug et al., 2017). Smaller values are associated with better performance. Error bars represent the within subject standard error of the mean. While the right hand taps more precisely in fast tapping, the left hand demonstrates lower timing variability in the slow tapping condition. The interaction between hand and condition is significant at $p = 0.003$. Note the overall higher precision in fast compared to slow tapping (differently scaled y-axes; Repp (2005)).

There was a main effect of condition ($F(1,41) = 108.54$, $p < 0.001$) with an overall higher precision in fast ($M = 13.85$ ms, $SD = 2.80$ ms) compared to slow tapping ($M = 32.74$ ms, $SD = 16.90$ ms) (Repp, 2005).

3.3.2 Slow tapping activates the right auditory association cortex

In fMRI, compared to silent baseline, both slow and fast bimanual tapping showed comparable activation patterns of bilateral regions involved in auditory-paced finger tapping, including the primary hand motor cortex, the dorsal and ventral premotor cortex, SMA, the cingulate motor area, parietal operculum, superior temporal cortex including the auditory cortex, posterior superior temporal gyrus and sulcus, the putamen, thalamus, and the superior cerebellum ($p < 0.05$, FWE cluster-level corrected, see Figure 3.4).

Activity in the auditory association cortex was right lateralized during slow compared to fast tapping ($p < 0.001$, FWE cluster-level

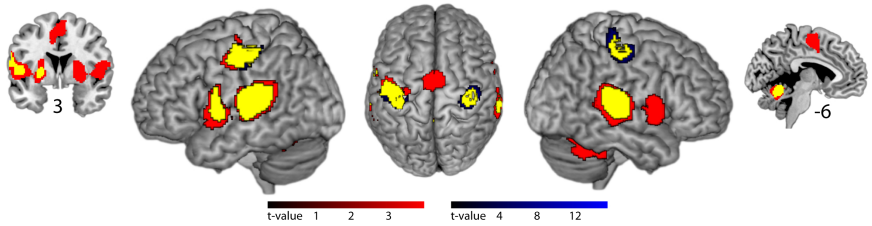

Figure 3.4: Brain areas activated by rhythmic finger tapping. Red: BOLD activation associated with slow tapping ($p < 0.05$, FWE cluster-level corrected). Blue: BOLD activation associated with fast tapping ($p < 0.05$, FWE cluster-level corrected). Yellow: Overlap of activity associated with slow and fast tapping. 3 and -6 indicate coronal and sagittal coordinates, respectively.

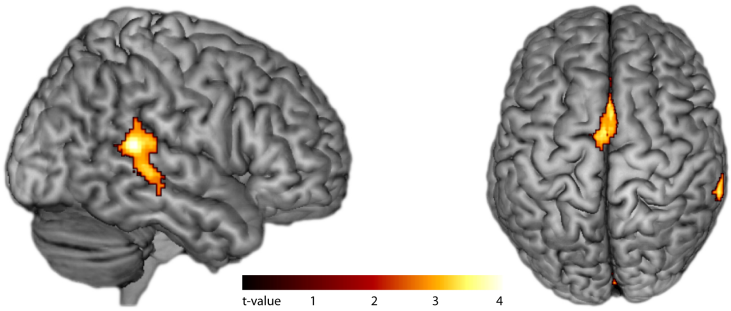

Figure 3.5: Effects of internal generation of a slow rhythm. BOLD activation for slow compared to fast tapping ($p < 0.05$, FWE cluster-level corrected). Activity in the auditory association cortex is right-lateralized at $p < 0.001$.

corrected, cluster size 395 voxels) and this was the only cortical patch that showed lateralized activity (all other $p > 0.05$, FWE cluster-level corrected). Generation of the slow rhythm activated additionally the bilateral fronto-mesial cortex including the SMA (see Figure 3.5 and Table 3.2).

3.3.3 Rhythms are differently represented in the left and right auditory association cortex

fMRI revealed a higher activation in the SMA and right auditory association cortex for slow compared to fast tapping. Thus, MEG power spectral densities of both sources, as well as left auditory asso-

ciation cortex, were tested for differences between simple auditory-motor synchronization and additional internal generation of the slow rhythm. In all three areas (SMA and both auditory association cortices), slow compared with fast tapping increased power in the low [14 - 20 Hz] and high beta band [21 - 30 Hz] but not in the delta, theta, alpha, or gamma range (see Table 3.3).

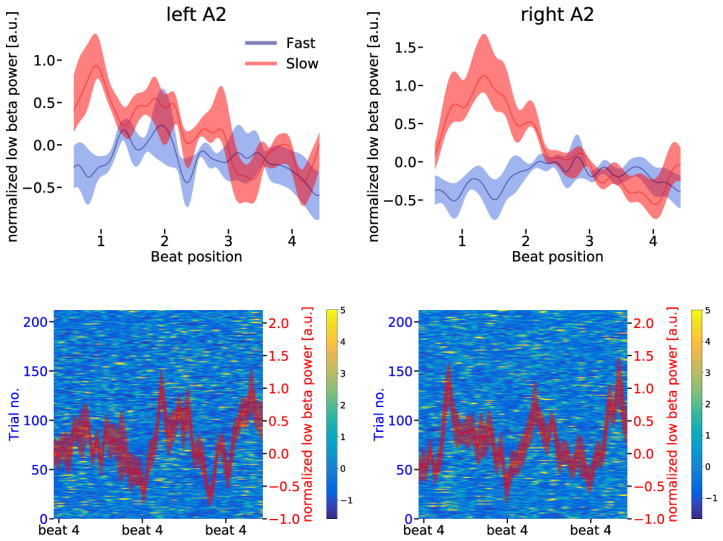

Figure 3.6: Upper panels: Low beta band (14-20 Hz normalized to mean over conditions) power modulation in the left (upper left panel) and right (upper right panel) auditory association cortex (A2) for slow (red) and fast (blue) tapping. One sequence of four auditory beats is illustrated. There was a stronger representation of the fast auditory beat frequency in the left compared to the right auditory association cortex during slow finger tapping (for statistics in the spectral domain, please see main text). Data are aligned to the tap at beat position four. Note the different scales for the beta power in left and right auditory association cortex. Shaded error bars represent the standard error of the mean (SEM). Lower panels: The background illustrates the low beta power in single slow tapping trials. Two sequences of four auditory beats with taps at beat position four are illustrated. Red curves represent mean low beta power ± SEM. Data are aligned to the right beat four in the panels.

Condition differences were stronger in the low compared to the high beta band in the SMA and in the right A2 (SMA: $t(16) = 3.033$,

$p = 0.002$, $p = 0.818$, right A2: $t(16) = 1.907$, $p = 0.046$), but not in the left A2 (left A2: $t(16) = 0.228$), a region that did not show condition effects in the fMRI. This confirms a more pronounced role of the low compared to the high beta band in rhythm generation (Gompf et al., 2017; Fujioka et al., 2015). Further analyses were therefore focused on the low beta band. The internal generation of the slow rhythm during slow tapping increased low beta power compared to fast tapping, during which beta power was strongly suppressed, in both auditory association cortices (main effect of condition $F(1,16) = 7.267$, $p = 0.011$, permutation ANOVA on mean values over the low beta band). Notably, low beta power condition differences between slow and fast tapping were larger in the right compared to the left auditory cortex (interaction between condition and hemisphere $F(1,16) = 3.460$, $p = 0.045$) possibly explaining the right-lateralized activation of this cortical region in fMRI. During slow tapping, low beta power was maximal at beat position one and decreased to maximal beta suppression at the tap on beat position four in both the left and right auditory association cortex (red curves in Figure 3.6). While this temporal modulation that reflected the rate of the internally generated slow rhythm was observed in both the left and the right auditory association cortex, the additional temporal modulation at the relative fast auditory beat frequency (2.5 Hz) was stronger in the left than in the right auditory association cortex (red curve in Figure 3.6, upper left panel).

In the spectral domain, this translated to a stronger temporal modulation at the fast auditory beat rate in the left compared to the right auditory cortex during slow tapping ($t(16) = 1.8956$, $p = 0.037$). In contrast, low beta power modulation at the slow tapping rate was stronger in the right compared to the left auditory association cortex ($t(16) = 1.636$, $p = 0.040$). In the fast tapping condition, during which participants actively tapped to every auditory beat,

beta power was maximally suppressed during the entire sequence of four beats (blue curves in Figure 3.6, upper panels). Consequently, decreases at the single beat positions were less pronounced (Kilavik et al., 2013).

3.3.4 Low beta amplitude modulation in the motor cortices reflects motor output

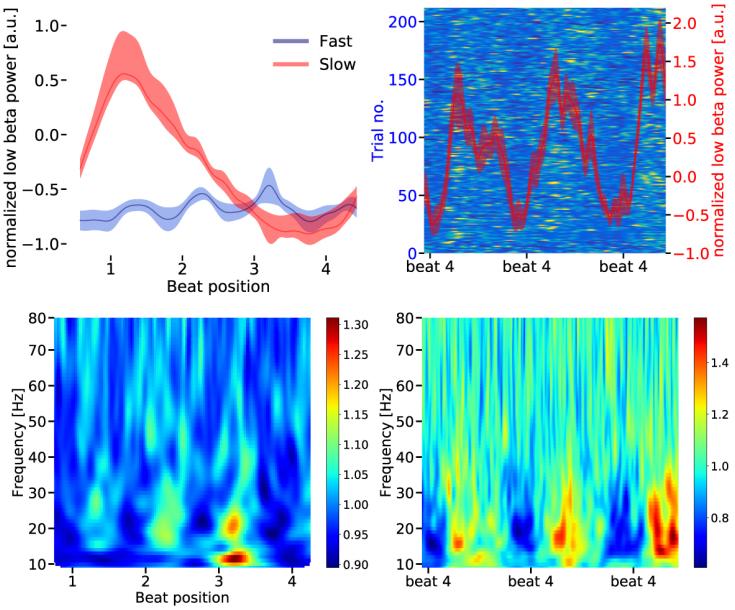

Figure 3.7: Upper left panel: Low beta band [14-20 Hz] power modulation in the supplementary motor area (SMA) for slow and fast tapping (mean over sequences). During fast tapping (blue) the low beta power is modulated by the fast tapping rate while during slow tapping (red) there is a temporal modulation by the slow tapping rate (linear beta power decrease). Data are aligned to tap at beat position four. Shaded error bars indicate the standard error of the mean (SEM). For statistics in the spectral domain, please see main text. Upper right panel: The background illustrates the low beta power in single slow tapping trials. Two sequences of four auditory beats with taps at beat position four are illustrated. Data are aligned to the tap at the right beat position four in the panels. Same scale as in Figure 3.6. Red curves represent mean low beta power ± SEM. Lower panels: Time frequency representation of the SMA source signal during fast (left panel) and slow tapping (right panel).

Power in the low beta band was also less suppressed in the SMA

during slow compared to fast tapping ($t(16) = 2.0917$, $p = 0.002$; dependent sample permutation t-tests on mean values over the low beta band). In contrast to the auditory cortices, temporal modulation of the low beta power envelope reflected the actual tapping rates (see Figure 3.7).

While auditory-motor synchronization in fast tapping decreased low beta power at every beat position, low beta power in the SMA decreased linearly from start of the sequence to the fourth beat position in the slow tapping condition. Consequently, the SMA spectrum contained a strong peak around 0.625 Hz (amplitude = 0.357 a.u.), but no peak at 2.5 Hz during slow tapping. During fast tapping there was a strong modulation at 2.5 Hz (amplitude = 0.695 a.u.) and only a very weak modulation around 0.625 Hz (amplitude = 0.058 a.u.). We further investigated whether the signal in the primary hand motor cortices and the cerebellum resembled the one observed in the SMA. Low beta amplitude modulation at auditory beat frequency during slow tapping did not differ between primary hand motor areas and the SMA (left M1: $t(16) = 1.217$, $p = 0.133$, right M1: $t(16) = 0.910$, $p = 0.182$), between the left and right hand motor cortex ($t(16) = 0.899$, $p = 0.332$) or between the cerebellum and the SMA (left cerebellum $t(16) = 1.386$, $p = 0.095$, right cerebellum $t(16) = 1.223$, $p = 0.110$). Together, in contrast to the auditory association cortices, the primary hand motor cortices, cerebellum and the SMA coded solely the motor output in the amplitude modulation of low beta oscillations.

3.3.5 Low beta band power modulations explain timing variability

If indeed the low beta power modulation reflects internal timing during slow tapping, it should predict timing variability in single trials. To investigate low beta band differences between short and long inter-tap-intervals during slow tapping, a permutation cluster

statistic was used to check for effects of timing variability.
Low beta power modulation in the left auditory cortex did not contribute to timing variability during slow tapping (Figure 3.8, leftmost panel). In the right auditory association cortex, the amplitude modulation during too long inter-tap-intervals was larger compared to the power modulation during too short inter-tap-intervals in the sense that low beta power was enhanced at beat position one when participants produced a too long inter-tap-interval (Figure 3.8, left middle panel, significant cluster at 560 - 660 ms, p = 0.042).

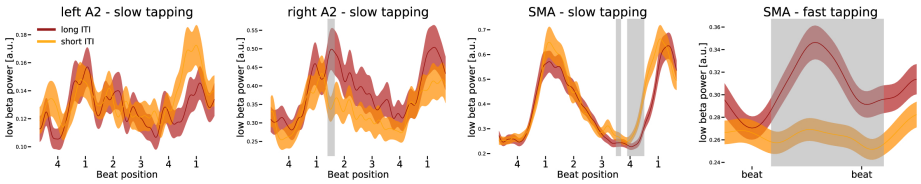

Figure 3.8: Differences in low beta power modulation between too short and too long inter-tap-intervals (ITI). Sequences of four auditory beats with taps at beat four were aligned at the left tap in the first three panels. While the fist three panels illustrate effects during slow tapping, the right panel illustrates low beta power in the supplementary motor area (SMA) during fast tapping (data left aligned). Significant differences between too long and too short sequences were marked in grey. Only low beta power in the right auditory association cortex (A2) and in the SMA predicted performance during slow tapping. Low beta amplitude coded the ITI in the SMA. Note the different scales in the panels.

In the SMA, low beta amplitude at beat position one did not influence performance during slow tapping significantly. Instead, too long inter-tap-intervals during slow tapping were associated with a longer low beta suppression at the end of the sequence coinciding with the delayed tap (Figure 3.8, right middle panel, significant cluster at 1400 - 1470 ms, p = 0.033; significant cluster at 1560 - 1800 ms p = 0.001). During fast tapping, low beta amplitude coded performance. A permutation analysis on fast tapping sequences revealed amplitude coding with enhanced beta power modulations for too long inter-tap-intervals and reduced beta power modulations

for too short inter-tap-intervals (Figure 8, rightmost panel, p = 0.002). Due to the maximal low beta suppression in auditory cortices during fast tapping, no significant difference between too long and too short inter-tap-intervals was observed in these regions.

3.3.6 Auditory-motor interactions

To study the contribution of auditory-motor interactions to the right-lateralized processing of the slow rhythm during slow compared to fast tapping, time-resolved partial directed coherence (TPDC) was calculated between the secondary auditory cortices and the SMA and vice versa on MEG source level data. This measure is insensitive to local power differences (Kaminski et al., 2016; Tsapeli and Musolesi, 2015; Nalatore et al., 2007; Muthuraman et al., 2018) and is ideally suited to investigate time-resolved directed functional connectivity. Both slow and fast tapping increased TPDC between the auditory cortices and the SMA in the low beta and mid gamma range with strongest effective connectivity from the left auditory association cortex to the SMA (see Figure 3.9).

To reveal directed connectivity when representing two rhythms instead of one rhythm, we focused the connectivity analyses on the contrast between slow and fast tapping and restricted them again to the low beta band (Gompf et al., 2017; Fujioka et al., 2015).
A two-factor repeated measures ANOVA on averaged connectivity in the low-beta band across hemisphere (left and right) and direction (auditory to motor and motor to auditory) revealed a main effect of hemisphere ($F(1,16) = 7.00$, $p = 0.018$) with stronger condition differences between slow and fast tapping in the left ($M = 0.007$, $SD = 0.0048$) compared to the right ($M = 0.003$, $SD = 0.0054$) hemisphere. This surprising effect was accompanied by a close-to-threshold interaction between direction and hemisphere ($F(1,16) =$

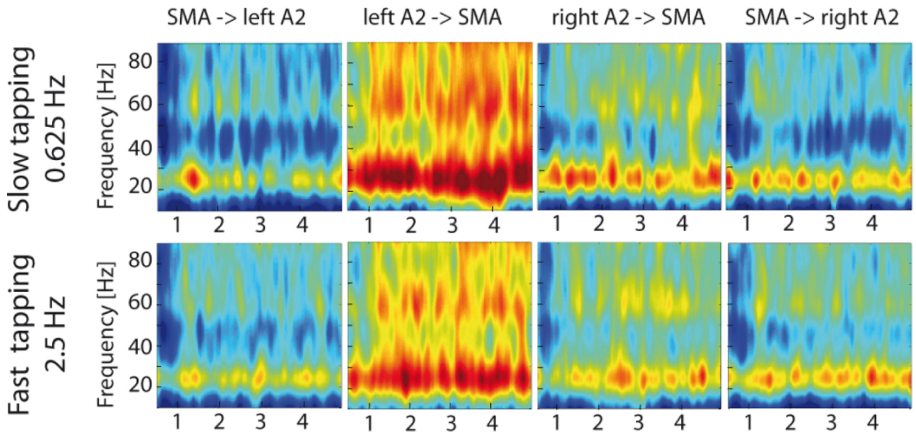

Figure 3.9: Time resolved partial directed coherence (TPDC) during slow (upper panels) and fast tapping (lower panels). TPDC was particularly strong in the low beta and the low gamma band. Note the overall increased connectivity strength between the left auditory association cortex and the SMA compared to the other connections. SMA: supplementary motor area. A2: Auditory association cortex.

3.83, p = 0.068). While the connections from left A2 to the SMA (t(16) = 4.174, p = 0.002), from the right A2 to the SMA (t(16) = 2.988, p = 0.005), and the one from the SMA to the left A2 (t(16) = 3.385, p = 0.001) increased low-beta connectivity for slow compared to fast tapping, the connection from the SMA to the right A2 was not enhanced for slow compared to fast tapping (t(16) = -0.882, p = 0.392, see Figure 3.10, left panel).

In sum, slow compared with fast tapping increased interactions in the low beta band between both the left and right auditory association cortex and the SMA and between the SMA and the left auditory association cortex (see Figure 3.10, right panel) with an overall stronger connectivity in the left compared to the right hemisphere. We investigated individual timing variability in the slow tapping condition for a correlation with directed connectivity contrasts for slow > fast tapping. An increased connection strength in the connection from the SMA to the left A2 during slow compared

to fast tapping correlated with timing variability in the sense that it reduced timing variability of the right hand when tapping slowly (r = -0.490. p = 0.04). All other correlations were not significant (p > 0.05). Auditory-motor interactions were not only structured in frequency, but also in time (see Figure 3.9).

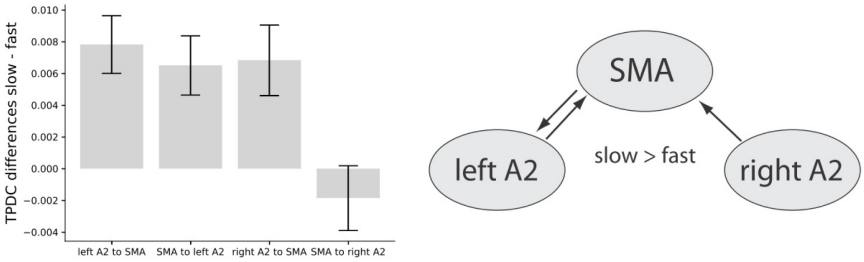

Figure 3.10: Left panel: Condition differences between slow and fast tapping in low beta band [14-20 Hz] effective connectivity. Connections with increased low beta band interactions (p < 0.05) during slow compared to fast tapping. SMA: supplementary motor area. A2: Auditory association cortex. TPDC: Time-resolved partial directed coherence.

The effective connectivity in the low beta range for slow compared to fast tapping was amplitude-modulated by a theta rhythm at 6.5 Hz in all connections except for the connection from the SMA to the right auditory association cortex (for statistics see Table 3.1), the connection that also did not show significant low beta band condition effects. There was an additional modulation of effective connectivity in the low beta range by an alpha rhythm at 10.5 Hz in all connections except for the connection from the right auditory cortex to the SMA. There was no other rhythmic modulation of low beta effective connectivity for slow compared to fast tapping (all p > 0.05).

3.4 Discussion

Our experiments identify the auditory association cortex as the part of the brain that represents relative rhythms differently in the two

hemispheres. During auditory-paced slow bimanual tapping, when two interrelated rhythms have to be represented by the brain, the left auditory association cortex represents the fast auditory beat rate more strongly than the right auditory association cortex in an amplitude modulation of low beta oscillations, although both auditory cortices receive identical sensory input. While both auditory association cortices represent also the internally generated slow tapping rate in an amplitude modulation of low beta power, the right auditory association cortex increases low beta power more strongly for slow compared to fast tapping and activates more strongly in terms of BOLD than the left auditory association cortex. This suggests that the brain represents the faster rhythm preferentially in the left and the slower rhythm preferentially in the right hemisphere which ultimately results in different tapping precision of the left and right hand during slow and fast tapping, respectively.

3.4.1 Rhythm representations in the auditory association cortices

A functional lateralization in terms of differences in activation of functional homologues was only observed in the auditory and not in the motor association cortices. Together with the cerebellum, motor cortices rather mirrored the actual motor output with a stronger BOLD signal in the bilateral SMA associated with reduced beta suppression during internal timing compared to auditory-motor synchronization (Gompf et al., 2017). Beta suppression during slow tapping was not maximal such that ceiling levels cannot explain missing lateralization in the SMA. Lateralization in motor association cortices is often observed in the lateral dorsal premotor cortex, particularly during asymmetric or complex bimanual actions as compared to the symmetric finger taps used in this study (Haslinger et al., 2002; Hlustk et al., 2002; Hardwick et al., 2013). The lateral dorsal premotor cortex is activated by polyrhythmic external stimuli

while internally generated rhythms activate the SMA (Swinnen and Wenderoth, 2004). The lack of lateralization effects in the motor cortices in our study suggests that the observed functional lateralization on the behavioral level was timing-related and not related to bimanual motor coordination (Serrien et al., 2003).

Indeed, right lateralization of auditory association cortex activity was related with improved left hand timing despite a bilateral activation of the SMA in slow tapping. No other brain areas beyond the bilateral SMA and the right auditory association cortex activated significantly for slow compared with fast tapping, a condition that could have been associated with increased counting effort compared to the fast tapping condition. Counting during perceptual grouping activates the intraparietal sulcus, dorsolateral prefrontal and inferior frontal cortex (Ansari, 2008), none of which was activated in our study. Our results confirm a strong contribution of the sensory cortices to the lateralization of action control, as suggested by the sensory-driven hypotheses on hemispheric specialization (Minagawa-Kawai et al., 2011; Ivry and Robertson, 1998). Because both auditory cortices receive the same auditory input (the fast auditory beat rate) in both slow and fast tapping, the nearly absent fast auditory beat rate representation in the right auditory association cortex likely constitutes the consequence of dynamic attention to every fourth auditory stimulus. Notably, this filtering is performed in the temporal domain, suggesting that the right auditory association cortex actively selects the relevant auditory beats for slow rhythm generation. This is reminiscent of the dynamic attending theory (Jones, 1987) which proposes that during perception, auditory cortex oscillations are aligned to rhythmic auditory input to select behaviorally relevant input (Schroeder and Lakatos, 2009). Beta power in the right but not in the left auditory association cortex explained timing variability during slow tapping. The internal

generation of a too slow rhythm was associated with an even larger amplitude modulation with enhanced beta power at beat position one. The same amplitude coding was observed in the SMA, although only during fast tapping. In our experiment, time information was coded in the amplitude of beta oscillations. Recently, time information during rhythmic finger tapping in the subsecond range has also been related to the amplitude of abstract representations of the SMA neural population dynamics in non-human primates (Gamez et al., 2019). Neither did the neuronal population dynamics scale in time, nor was the slope of the beta power modulation in our study modulated by slow vs. fast finger tapping, which suggests time indeed is coded in amplitude, at least during rhythmic finger tapping (see Fujioka et al. (2015) and Wang et al. (2018) for contrasting views).

Assuming time information is coded accumulator-like (Ivry and Richardson, 2002) in the power difference between minimal and maximal beta suppression we may state that amplitude coding identifies brain regions with different preferred time intervals. The association between timing variability and amplitude coding in the motor association cortex during fast tapping and the relationship between timing variability and amplitude coding in the right but not left auditory association cortex during slow tapping confirms that the brain uses the motor system for subsecond timing and non-motor cortices for suprasecond timing (Morillon et al., 2009). During slow tapping the SMA coded solely the information on the actual timing of the tap in the latency of the maximal suppression at beat position four. This emphasizes the contribution of the right auditory association cortex to the internal generation of a slow, supra-second rhythm.

Low beta power in the cerebellar sources did only mirror the motor output in our experiment. However, subcortical regions including the cerebellum, basal gangia and thalamus, make part of a ded-

icated neural timing system and likely provide more than motor timing information (Kotz and Schwartze, 2011). We cannot rule out that other cerebellar sources with less cortico-muscular coherence compared to the cerebellar sources identified here show internal timing-related profiles.

3.4.2 Polyrhythmicity during syncopation activates the right auditory association cortex

Although the right auditory association cortex was more strongly activated by the slow than the fast tapping condition, also the left auditory association cortex represented the slow tapping rate in a beta power decrease from start to the end of a sequence of four auditory beats. This raises the question why the right auditory association cortex was additionally recruited for slow tapping and associated with performance if all necessary temporal information could be decoded from left auditory association cortex. Note that in our study participants tapped the slow rhythm on every fourth auditory beat, which represents a syncopated rhythm with a 270° phase delay in relation to the 4/4 standard meter that was introduced by the four priming auditory beats prior to each trial. In a previous behavioral experiment, we showed that the right hemisphere advantage for the control of slow tapping depended on syncopation, because it was not observed when participants tapped at auditory beat position one when tapping slowly (at 0° phase difference relative to the standard meter, Pflug et al. (2017)). Non-syncopated slow tapping at beat position one reflects the overlearned 4/4 meter that constitutes the standard meter in Western culture (London, 2012). In dynamic pattern theory, 0° phase angles represent more stable dynamical states compared to 270° phase differences (Zanone and Kelso, 1992).

Perceiving syncopated compared to non-syncopated rhythms activates the right more than the left auditory association cortex (Her-

dener et al., 2014). However, our results are not a consequence of stimulus features like accentuation or lengthening, because the auditory stream used in this experiment consisted of identical beats. They rather indicate that the involvement of the right auditory cortex is not a direct consequence of the increased complexity of rhythmic grouping during syncopated slow tapping compared to simple auditory-motor synchronization during fast tapping. Instead, the MEG and behavioral results demonstrate that the two rhythms are not represented randomly in the left and right hemispheres, but rather systematically with a stronger representation of the relative fast rhythm in the left and of the relative slow rhythm in the right hemisphere.

We interpret our observation in such a way that syncopated rhythms are represented separately by the two hemispheres as long as they are not yet hierarchically integrated in a Gestalt based on experience. From a dynamic pattern theory perspective, the 270° phase angle during syncopated tapping induces competition between attractor states with a strong tendency to tap at 0° phase difference relative to the standard meter (Swinnen, 2002). This tendency could be reduced by increasing the energy needed for a phase transition from tapping the instructed 270° phase angle to the tapping along the standard meter. Note that in motor as well as auditory cortices, beta amplitude was minimal at beat position four and maximal at beat position one during slow tapping, which decreases tapping probability at beat position one. Competition between the standard meter and the phase-shifted slow tapping rhythm of same frequency could be reduced by increasing the physical distance of their representations. This would permit parallel representations of competing attractors. The brain could potentially solve this problem by representing the standard meter and its relationship to the fast auditory beat rate in the right hemisphere and the slow tapping rhythm in

the left hemisphere. The fact that the brain does not follow this path and rather represents the internally generated phase-shifted slow rhythm in the right auditory association cortex and the fast auditory beat rate in the left auditory association cortex speaks in favor of different temporal filters in auditory association cortex as sources of hemispheric specialization.

In addition, preferential binding of rhythms with different frequencies in the left hemisphere may contribute to functional lateralization. The left hemisphere outperforms the right hemisphere in local binding (Flevaris et al., 2010), which is critical for beat and meter integration. Integrating fast rhythms and slow rhythms with 0° phase angle relative to the standard meter may facilitate hierarchical binding in a Gestalt (Zanone and Kelso, 1992) which could bias meter processing to the left hemisphere. This may explain the numerous reports on an involvement of the left hemisphere in rhythm production in professional musicians (Vuust et al., 2006; Kunert et al., 2015; Herdener et al., 2014) and explain empirical findings that ostensibly support the motor-driven hypotheses of left hemispheric dominance (Kimura, 1993; Haaland et al., 2004).

3.4.3 Auditory-motor interactions in the beta range privilege the left hemisphere for rhythm integration

Tapping rhythms were most strongly represented in the low beta band in both motor and auditory cortices. Effects in the beta band have often been found in tasks that require synchronization of large-scale brain networks (Gehrig et al., 2012; Roelfsema et al., 1997) and more recently have been associated with top-down signals in hierarchically organized cortical networks (Bastos et al., 2015; Fontolan et al., 2014). Beta oscillations are particularly strong in the motor system including the basal ganglia, which also play an important role in rhythmic motor behavior (Kotz et al., 2009). During finger tapping, spike-field coherence in the striatum is stronger for

beta compared to gamma oscillations and beta oscillations are more strongly related with internal rhythm generation than with sensory processing during tapping (Bartolo et al., 2014). Consequently, an important role of auditory-motor interactions in the beta range was expected and, indeed, interactions between the auditory and motor association cortices were strongest in the low beta band. However, the internal representation of the slow tapping rhythm in the right auditory association cortex was not associated with additional top-down signals in the low beta band from the SMA to the right auditory association cortex compared to fast tapping during which no additional rhythm was represented.

In the right hemisphere, slow tapping increased information flow in the low beta band only from the auditory association cortex to the SMA, possibly to provide slow rhythm information. The SMA received also stronger low beta input from the left auditory association cortex during slow compared to fast tapping which could reflect the effort to integrate the slow with the fast rhythm that was more strongly represented in the left auditory association cortex. The SMA could thus be interpreted as the midline structure that integrates rhythm information from both auditory association cortices and times tapping accordingly. Yet, in contrast to the right hemisphere, slow tapping also strengthened the top-down connection from the SMA to the left auditory association cortex compared to fast tapping. This left-lateralized top-down connection was the only connectivity in our study that correlated with tapping accuracy. The stronger the connection was from the SMA to the left auditory association cortex during slow compared with fast tapping, the more precise participants tapped with their right hand in the slow tapping condition. This suggests that the right hand, that taps fast rhythms more precisely than slow rhythms, may benefit from bidirectional auditory-motor interactions in the left hemisphere when

tapping slowly. Together with the overall stronger directed connectivity between the left auditory association cortex and the SMA, this auditory-motor loop may facilitate rhythm integration in the left hemisphere (Nozaradan et al., 2015).

Auditory-motor loops can also be used to facilitate perceptual timing in the absence of overt motor behavior. Such a motor facilitation is efficient when estimating time periods of below one to two seconds (Morillon et al., 2009; Rao et al., 1997; Funk and Epstein, 2004). Auditory rhythmic sampling without overt motor behavior involves beta signals from the left lateralized motor cortex to the auditory association cortex (Morillon and Baillet, 2017). This finding confirms the left-lateralized top-down connection in beta connectivity between the motor and auditory association cortex found in our study even in the absence of overt movement.

Beta signals associated with slow compared to fast tapping between the auditory association cortices and the SMA and vice versa were modulated by a theta rhythm. Fronto-temporal theta oscillations have been associated with auditory-motor and multisensory integration (van Atteveldt et al., 2014) and more specifically support auditory working memory (Albouy et al., 2017), speech perception (Assaneo and Poeppel, 2018), and speech production (Behroozmand et al., 2015). The auditory-motor theta rhythm observed in this finger tapping study was observed at a peak frequency of 6.5 Hz, which corresponds to the frequency at which also the velocity of slow finger movements is modulated (Gross et al., 2002). This is slightly higher than the auditory-motor theta rhythm associated with speech processing, which peaks at 4.5 Hz (Assaneo and Poeppel, 2018), potentially due to the higher natural resonance frequencies of the fingers compared to the jaw (Junge et al., 1998).

3.4.4 Implications for speech processing

The observed functional differences between the hemispheres during auditory-paced finger tapping remind the asymmetries observed during speech processing. During speech perception, the syllable rate in the theta range serves as a strong acoustic cue that entrains oscillations in the bilateral auditory association cortex and induces auditory-motor interactions in this frequency range (Assaneo and Poeppel, 2018). Auditory-motor interactions are left-lateralized both during speech perception (Mottonen et al., 2014; Murakami et al., 2015; Hickok, 2015) and speech production (Kell et al., 2011; Keller and Kell, 2016) suggesting left-lateralized auditory-motor loops. In both motor and auditory association cortices, binding of speech-relevant rhythms via cross-frequency coupling is left lateralized in fronto-temporal cortices during speech perception (Gross et al., 2013). These observations suggest left-lateralized auditory-motor loops could improve rhythm integration by cross-frequency coupling both during speech perception and production. Indeed, reduced auditory-motor coupling in the left hemisphere of people who stutter is associated with overt deficits in controlling speech rhythm (Neef et al., 2015; Chang and Zhu, 2013; Kell et al., 2018). The deficit in rhythm integration in people who stutter is associated with an over-recruitment of the right hemisphere during speech production that is reduced upon recovery (Kell et al., 2009, 2018). The right over-activation during speaking may be regarded as a strategy to separate competing attractors that arise from insufficient auditory-motor mapping in the left hemisphere (Hickok et al., 2011). It is interesting to note in this context that this speech disorder that has been associated with basal ganglia dysfunction (Alm, 2004) shows abnormal beta oscillations associated with timing both in speech and non-speech tasks (Etchell et al., 2016, 2015). Future research will need to elucidate the commonalities and differences between the functional lateraliza-

tion of hand control and the lateralization of speech production.

3.5 Conclusions

We show here that representing two rhythms during syncopation lateralizes processing of the relative faster rhythm to the left and the relative slower rhythm to the right hemisphere. Auditory association cortices filter adaptively the preferred temporal modulation rate and send this time signal to the supplementary motor area for motor output coordination. The filter is relative rather than absolute, meaning that the hemispheres do not lose the complementary information, but nevertheless represent preferentially different rhythms. An additional top-down communication from the SMA to the left auditory association cortex may privilege the left hemisphere in integrating multiple rhythms in a multiplexed Gestalt, which likely represents a prerequisite for more complex cognitive functions like speech processing.

3.6 Methods

3.6.1 Participants

Twenty-five participants (10 male; aged 19 - 31 years; M = 24 years) were included in the fMRI study; seventeen participants (6 male, aged 21-38 years; M = 26 years) in the MEG study. Number of participants was chosen based on a literature research for finger tapping experiments in MEG/EEG studies and fMRI, respectively. Participants had normal or corrected-to-normal visual acuity, normal hearing, no neurological deficits and were right-handed according to self-reports and their laterality index based on the Edinburg inventory of manual preference (fMRI: M = 86; MEG: M = 89; Oldfield (1971)). Participants performed a test run of approximately five minutes before measurement to become familiar with the task. All participants gave written informed consent prior to the study and

were paid for participation. Experimental procedures were approved by the ethics committee of the medical faculty of Goethe university (GZ 12/14), and are in accordance with the declaration of Helsinki.

3.6.2 Tapping Paradigm

In every trial of this auditory paced finger tapping paradigm, 36 auditory beats (1600 Hz, 2 ms) were presented with a constant inter-beat-interval of 400 ms (2.5 Hz, 210 bpm). Participants were asked to tap with their index fingers at two different rates to these beats. No auditory feedback was provided. Thus, auditory input did not differ between conditions. In the fast tapping condition, participants tapped to every auditory beat. In the slow tapping condition, participants were instructed to iteratively count four beats internally and tap only on beat position four (Figure 3.1). Therefore, tapping to the 36 auditory beats resulted in 36 taps when tapping the fast rate and 9 taps when tapping the slow rate during each 15 second-long trial. Eight different tapping conditions were performed. In four unimanual conditions participants tapped with one hand (left or right) either the fast or the slow tapping rate. Four bimanual conditions were either performed monofrequent, in which both hands tapped the same rate or multifrequent, in which one hand tapped the fast rate and the other hand the slow rate. Here, we report the two bimanual monofrequent conditions during which both hands were engaged in the same motor output. While "fast tapping" represents simple auditory motor synchronization to the presented auditory beat, in "slow tapping" the single beats had to be cognitively grouped in sequences of four. This necessitates the generation of a slower rhythmic structure in addition to processing the same fast auditory beats as in fast tapping. The task was performed in runs with 24 trials each, in semi-randomized order. A trial started with a presentation of a visual instruction that indi-

cated the upcoming condition. Before participants started tapping, four auditory beats of higher pitch primed the auditory beat rate. The inter-trial interval was jittered in both recordings (fMRI: 10.1 - 13.6 s and MEG: 7.7 - 12 s) to reduce temporal predictability during baseline.

3.6.3 Timing variability

Timing variability was calculated using the standard deviation of absolute distance between the actual inter-tap-intervals and the target inter-tap-interval (400 ms for fast, 1600 ms for slow tapping rates) of consecutive taps (for a more detailed description see Pflug et al. (2017)). For tap detection, the maximal tap pressure was used. Timing variability was calculated for every hand and condition independently. Values of both recording methods (fMRI and MEG) were used as dependent variables in a 2 (condition [slow, fast]) x 2 (hands [left, right]) mixed design repeated measure analysis. Significant effects were post-hoc tested using paired-sample t-tests. Significance level (alpha) was set at 0.05. Statistical tests were conducted using SPSS Statistics 22.0 (IBM Company, RRID:SCR_002865).

3.6.4 fMRI

3.6.4.1 Recording procedure

Participants laid in a supine position. Two pneumatic pressure sensors (MP150, Biopac Systems, RRID:SCR_014279) were attached to the pads of participants index fingers and participants were asked to tap with the sensors on their ipsilateral thigh. The pressure sensitivity of the sensors was 0.01 cm H2O with a sampling rate of 1 kHz. Auditory beats were presented binaurally via headphones and visual condition cues were displayed with a projector on a screen in front of the participants. Pacing signals and visual instructions were presented with Presentation Software (Neurobehavioral Sys-

tems, Albany, CA, USA Albany). The fMRI experiment consisted of 2 runs, each including three trials of every condition in randomized order with a one minute break in between runs.

3.6.4.2 Data acquisition

The fMRI data were recorded in a simultaneous EEG/fMRI experiment; however, we only report the fMRI results in the present study. The results of the EEG analysis are presented in Gompf et al 2017. The entire equipment was fMRI compatible and met all security standards (Brain Products EEG/fMRI Hardware, RRID: SCR_009443). Scanning was performed on a Siemens Trio 3 Tesla magnetic resonance system (Siemens MAGNETOM Vision, Erlangen, Germany) equipped with a circular polarized Send/Receive head coil with an integrated preamplifier. Functional images were obtained with a gradient-echo T2*-weighted transverse echo-planar imaging (EPI) sequence (614 volumes; repetition time (TR) = 2.08s; echo time (TE) = 29ms; flip angle = 90°; 32 axial slices; 3mm3 isotropic voxel size). Additionally, high-resolution T1-weighted anatomical scans (TR = 2.25s; TE = 3.83ms; flip angle = 9°; 176 slices per slab; 1mm3 isotropic size) were obtained.

3.6.4.3 Preprocessing

Image processing and data analyses were performed in SPM12 (Welcome Trust Centre for Neuroimaging, London, UK; RRID: SCR_007037). After eliminating the first four volumes in each participant due to field inhomogeneity in the beginning of each run, standard preprocessing was performed (realignment, co-registration of anatomical T1-images to the mean functional image with subsequent segmentation using Tissue Probability Maps, normalization to the Montreal Neurological Institute [MNI] standard brain template and smoothing with an 8 mm full-width at half-maximum Gaussian kernel). For

lateralization analyses (see below), images were preprocessed with the use of a symmetrical template to prevent anatomical differences between hemispheres from inducing spurious lateralization effects (Keller and Kell, 2016). To this end, symmetric Tissue Probability Maps were created by averaging the mean Tissue Probability Map and its flipped counterpart. The preprocessed images were analyzed within the framework of general linear models for time-series data (Worsley and Friston, 1995).

3.6.4.4 Statistical Analysis

On the single-subject level, eight condition-specific regressors were modelled by convolving the onsets and durations of conditions (modelled by boxcar functions) with the canonical hemodynamic response function to obtain predicted BOLD responses. Additional fifteen regressors of no interest were calculated, eight of them capturing the variance associated with the condition instructions, one for modelling an additional tap participants usually made after the last metronome click in fast conditions, as well as six regressors for head-motion-related effects. For group-level analyses, the regressors of all eight conditions, modelling condition-specific tapping effects, were included in a 1 x 8 ANOVA to account for the variance caused by the other conditions. We report the effects of slow and fast bimanual tapping and thus contrasted the conditions separately against an implicit baseline and against each other. The significance threshold was set at $p < 0.05$ family-wise error (FWE) corrected at cluster level with a cluster identification threshold of $p < 0.001$, uncorrected.

3.6.4.5 Lateralization Analysis

Post-hoc lateralization analyses were performed on the effect of slow rhythm generation. The processing steps followed (Keller and Kell, 2016). First, contrast images of slow > fast tapping were calcu-

lated on the single subject level using the symmetrical template for normalization. These images were then flipped over their mid-sagittal axis. In a subsequent two-sample t-test, the non-flipped contrast images were compared with their flipped counterparts on the group-level. To avoid artifacts resulting from cerebrospinal fluid in the sagittal sulcus, a midline mask was applied. The threshold for significance was set at $p < 0.05$ FWE corrected at cluster level with a cluster identification threshold of $p < 0.001$. This identified significant activity differences between brain regions and their homotopes.

3.6.5 MEG

3.6.5.1 Recording procedure

Participants sat in an upright position in the MEG chamber. Head movements were limited using foam pads. Participants tapped on pressure sensors fixed on the left and right armrests. Auditory beats were presented binaurally through plastic tubes and a projector was used to display visual condition cues on a screen. Participants were asked to restrict their gaze to the center of the screen during the task. The experiment consisted of four runs, 11 minutes each, including each three trials of every condition, with two minutes breaks in runs. Surface electromyogram (EMG) electrodes were placed over both extensor digitorum communis muscles. Electrooculogram (EOG) was recorded to detect horizontal and vertical eye-movements and electrocardiogram (ECG) for heart beats. Participants' head positions relative to the gradiometer array were determined continuously using three localization coils (ear-channel and nasion).

3.6.5.2 Data acquisition

MEG was recorded using a whole-head system (Omega 2005; VSM MedTech) with 275 channels at a sampling rate of 1200 Hz in a

synthetic third-order gradiometer configuration. Data were filtered off-line with fourth-order Butterworth 300 Hz low-pass and 2 Hz high-pass filters. Line noise at 50 Hz was removed using a band pass filter. Recorded data were down-sampled to 1000 Hz and fused with the data of the tapping pressure sensors.

3.6.5.3 Preprocessing

MEG recordings were preprocessed and analyzed using the Fieldtrip toolbox (Oostenveld et al. (2011), RRID:SCR_004849) in MATLAB (RRID:SCR_001622). Trials containing muscle or SQUID artifacts were removed using an automatic artifact rejection algorithm (Delorme et al., 2004). Trial segments with a head movement exceeding 5 mm were also discarded from further analysis. Independent component analysis was performed to identify and reject components of heart muscle and blinks. For easier detection, components were correlated with the ECG and EOG signal. Data from whole trials were used for source reconstruction (see next section). Clean trials without artifacts (overall 89 %) were cut into sequences containing four consecutive beats. In the fast tapping condition, four consecutive taps were defined as a valid sequence. Sequences in the slow tapping condition were valid if they included only one tap at the intended beat position four. To visualize the slow rhythm over multiple sequences, we also cut trials into time windows containing two sequences of four auditory beats. To this end we used the taps of the fourth and fifth sequence within each trial, which are in the middle of in total nine sequences per trial. An overview of the following analysis steps is illustrated in Figure 3.2 and explained in detail below.

3.6.5.4 Source reconstruction

We identified brain areas that showed significant coherence with the averaged EMG signals of the extensor digitorum muscles during bimanual fast tapping following the standard procedure for source analysis during auditory paced finger tapping (see Figure 3.2 step 1, Gross et al. (2001); Pollok et al. (2005); Muthuraman et al. (2014, 2018)). A spherical MEG source model was used to estimate the sources in every participant. Afterwards, cortico-muscular coherence was calculated and significant sources were identified for every participant individually.

In detail, a dynamic imaging of coherent sources (DICS) beamformer approach was used to identify (sub-)cortico-muscular coherent sources. For beamforming, the individual head models were co-registered with the Talairach standard MRI brain using Fieldtrip. MEG source analysis with a spherical head model and further source reconstruction based on a template brain is accurate (Steinstraeter et al., 2009) and constitutes the standard approach when individual structural MRI data are not available for every participant (Jensen et al., 2005; Ross and Tremblay, 2009; Fujioka et al., 2010, 2015), because the spatial precision of detected sources is equivalent to analyses based on individual structural MRI data (Hasnain et al., 1998). Since significant coherent sources were identified in each individual, the topographical relationship between sources was additionally considered in source denomination.

Original coherence was tested against 999 surrogate datasets where the MEG trial structure was shuffled but the EMG trials were kept stable. For every grid point, a threshold for detecting coherent sources was set at the 95th percentile of permutation results. This analysis revealed cortical and subcortical brain areas involved in bimanual finger tapping in each participant, including the supplementary motor area and thalamus, as well as the bilateral dorsolateral

prefrontal cortex, dorsal premotor cortex, primary hand sensorimotor cortex, secondary somatosensory cortex in the Rolandic operculum, posterior parietal cortex, secondary auditory cortex in the superior temporal gyrus, and cerebellum. Since the activation of the right hand motor cortex in bimanual fast tapping was sub-threshold in some participants (above 90th percentile), the unimanual left hand fast tapping condition was used to confirm the localization of the right hand motor cortex above significance level.

3.6.5.5 Source level analysis

As a next step, time courses of EMG-coherent sources were extracted separately for the slow and fast bimanual tapping condition using a linearly constrained minimum variance beamformer method (LCMV, Van Veen et al. (1997)) for each frequency from 2 - 300 Hz (temporal resolution: 1000 Hz, see Figure 3.2 step 2). Source level analyses were performed on extracted timeseries of the SMA and the right auditory association cortex, since these areas were identified by fMRI as being activated in slow compared to fast tapping. To compare activity in the right auditory cortex with activity in its homologue, activity in the left auditory association cortex was also extracted. For completeness, also activity in the left and right primary handmotor cortex, as well as activity in both cerebellar hemispheres was investigated.

All signals were converted into the time-frequency space. Wavelet transformations (slepian windows) were calculated for every sequence by sliding a window of 7-times the related period length (2-80 Hz, 1 Hz resolution) in 10 ms steps. Averages over sequences of four auditory beats were calculated for every participant and condition, resulting in two dimensional arrays with time and frequency dimensions (see Figure 3.7, lower panels for examples). Power averages over frequencies were calculated in predefined standard frequency

bands: theta [4-7 Hz], alpha [8-13 Hz], low beta [14-20 Hz], high beta [21-30 Hz] and gamma [31-80 Hz]. To compare power spectral differences (PSD) between conditions within cortical sources, frequency bands were averaged over the time domain resulting in one PSD value per condition and participant. These values were used in non-parametric permutation dependent t-tests (999 permutations, alpha = 0.05) to detect condition differences in the amplitude of the predefined frequency bands. Additionally, t-contrasts between conditions from the sources of interest (SMA and auditory cortices) were calculated to test for power differences between the low and high beta band. Since condition contrasts were higher in the low compared to the high beta band, we focused further analysis on the low beta band (Figure 3.2, step 3), which has been shown to reflect internal timing best (Fujioka et al., 2015; Gompf et al., 2017).
Band-pass filtered low beta band signals in the SMA and auditory association cortex were normalized with the average over both conditions to reduce inter-subject-variability and plotted as a function of time during the sequence of four auditory beats, separately for the slow and fast tapping condition. To detect an amplitude modulation of the low beta band signal (Morillon and Baillet, 2017; Fujioka et al., 2015) at a temporal modulation rate that corresponded to the fast auditory beat rate (2.5 Hz), a fast Fourier transformation was applied to the normalized band-pass signals (resulting frequency resolution: 0.5 Hz). Power spectra of each source were z-transformed for every participant. PSD values of low-beta band modulation at auditory beat frequency (2.5 $\pm$ 0.5 Hz) were tested for differences between the left and the right auditory cortex as well as between the left and right primary hand motor cortex and between the primary handmotor cortices and the SMA, and between left and right cerebellum and the SMA using non-parametric permutation dependent t-tests (999 permutations, alpha = 0.05). Since sequences of

four taps did not allow for analysis of a temporal modulation rate at 0.625 Hz, we additionally investigated entire trials for a temporal modulation of low beta power at the slow tapping rate (0.625 Hz). PSD values of low-beta power modulation at the slow tapping frequency (0.625 ± 0.25 Hz) were tested for condition differences in the left and right auditory cortices as well as in the SMA (non-parametric permutation dependent t-tests, 999 permutations, alpha = 0.05). We additionally tested whether the representation of the slow tapping rate in the spectrum of the right auditory association cortex was stronger compared to the left auditory association cortex (non-parametric permutation dependent t-tests, 999 permutations, alpha = 0.05).

Single trial data of slow tapping are illustrated in Figure 3.6, lower panels and Figure 3.7, upper right panel. Averages of beta power sequences are plotted in Figure 3.6, upper panels, and Figure 3.7, upper left panel. The lower panels in Figure 3.6 and the right upper panel in Figure 3.7 illustrate the average beta power during two sequences of slow tapping for better illustration of the slow rhythm.

3.6.5.6 Relationship between low beta power modulation and timing variability

To investigate the relationship between the low beta band activity and inter-tap-intervals (ITI), source data of the SMA, left auditory cortex and right auditory cortex was used. ITIs for the slow tapping condition ranged from 1384 to 1816 ms, for the fast tapping condition ITI range was from 268 to 568 ms. Sequence data in the slow tapping condition (4 beats) were cut from the time point of maximum pressure - 500 ms and + 2500 ms to include also too long intervals. Low beta power over time was extracted and sequences were split into sequences with long ITIs (ITI > 66th percentile), n = 517, medium ITIs (33 th percentile < ITI < 66th percentile), n

= 1567 and short ITIs (ITI < 33th percentile), n = 517. The same procedure was performed for fast taps.

For investigating effects at the end of the sequence, the ITI range of 400 ms was used for comparison. To investigate effects at beat position one, the time of the mean beta peak in the medium ITI trials (500 ms after the tap for slow and 220 ms after the tap for fast) was used as the center point for a second window spanning also 400 ms. Long and short ITI sequences were compared in these two windows using a non-parametric independent permutation t-test with cluster correction (alpha at 0.5).

3.6.5.7 Time-resolved partial directed coherence

Using a time-frequency causality method allows analyzing the temporal dynamics of causality with frequency resolution (Figure 3.2 step 4). The time-resolved partial directed coherence (TPDC) is based on dual-extended Kalman filtering (Wan and Merwe, 2002), and allows time-dependent auto-regressive coefficients to be estimated, independent of the underlying frequency power in the time-series. At each time point, previous state and weight estimates were fed to both the Kalman filters. Both predictors were then corrected on the basis of observed data such that they yield current state and weight estimates. By using two Kalman filters working in parallel with one another, both states and model parameters of the system were estimated at each time point. The time-dependent multivariate autoregression (MVAR) coefficients were used to calculate the causality between the time series. By calculating the time-dependent MVAR coefficients at each time point, partial directed coherence (PDC, Blinowska (2011)), based on the principle of Granger causality, was computed.

Based on the fMRI results with increased activity in the right but not the left auditory association cortex and the SMA for slow com-

pared to fast tapping, the Fourier transform of the MVAR coefficients and PDC was calculated between the SMA and the left and right auditory association cortices, respectively, resulting in two auditory-motor and two motor to auditory connections. TPDC was calculated for every sequence individually. Afterwards, slow and fast sequences were averaged separately. This resulted in 2000 time points and 161 frequency bins (1-80 Hz). The first 200 time points were not used for further analyses due to the Kalman filter adaptation period.

Values of directed connectivity were validated with a reverse technique that tests for effects of volume conduction (Haufe et al., 2013). We compared original connectivity with reversed connectivity. This analysis did not show significant differences between original and reversed connectivity in a permutation t-test ($p > 0.05$), which excludes volume conduction effects.

Like the analyses of the source signals, further connectivity analyses were also focused on the low-beta band. Therefore, the time-frequency representation of the connectivity analysis was reduced by extracting the average over frequencies in the low-beta band. The band pass filtered signal was smoothed with an average mean filter of 100 ms windows with 10 ms steps.

Connectivity results were tested on power differences in the low beta band and focused again on the difference between slow and fast tapping. For power differences, contrasts between slow and fast tapping were tested in a 2 factorial non-parametric permutation ANOVA with factors hemisphere (left and right) and direction (auditory to motor and motor to auditory, with motor cortex being represented by the SMA). Alpha was set to 0.05.

To detect temporal modulations of low beta TPDC, the band-pass filtered signal was transformed into Fourier space. Resulting power spectra were normalized by subtracting the axis distance for ev-

ery subject, and z-transformed. Frequency peaks in the overall 1/f distribution were validated following Haller et al. (2018). The algorithm uses automatic parameterization of neural power spectral densities as a combination of the aperiodic signal and putative periodic oscillations with no a priori specification of band limits.

To investigate the relationship between directed connectivity and behavioral parameters, timing variability in the slow tapping condition was correlated using Pearson's correlation coefficient with the significant connectivity contrasts (slow > fast). Alpha was set to 0.05.

Table 3.1: Rhythmic modulation of the low beta band directed connectivity in slow compared to fast tapping.

Connection	**Modulation peak in theta band**	**Modulation peak in alpha band**
left A2 to SMA	$t(16) = 2.441$, $p < 0.001$	$t(16) = 1.803$, $p = 0.031$
right A2 to SMA	$t(16) = 2.305$, $p = 0.001$	$t(16) = 1.399$, $p = 0.114$
SMA to left A2	$t(16) = 2.760$, $p = 0.004$	$t(16) = 2.398$, $p = 0.002$
SMA to right A2	$t(16) = 1.509$, $p = 0.083$	$t(16) = 2.093$, $p = 0.010$

Table 3.2: FMRI effects of Slow Rhythm Generation (slow > fast). BA, Brodmann area; L, left hemisphere; R, right hemisphere.

Anatomical region	**Cluster p-value**	**Cluster size**	**Local maxima**	**BA**	**Peak MNI-coordinates (x,y,z)**
Frontal	0.000	1087	R Supplementary Motor Area	6	[4 8 52]
			L Supplementary Motor Area	6	[-10 -2 54]
			L Superior Frontal Gyrus	6	[-20 -4 54]
			R Middle Cingulum	24	[2 14 38]
			R Anterior Cingulum	24	[4 28 24]
Temporal	0.001	619	R Superior Temporal Gyrus (A2)	42	[62 -38 14]
			R Middle Temporal Gyrus (A2)	21	[46 -38 2]
Occipital	0.000	925	R Calcarine Sulcus	18	[4 -88 -8]
			R Lingual Gyrus	18	[6 -74 -4]
			L Lingual Gyrus	18	[-4 -72 -4]

Table 3.3: MEG source power for fast (f) and slow (s) tapping (Mean/Standard Deviation).

Freq. band	**SMA**	**Left A2**	**Right A2**	**Left M1**	**Right M1**	**L cerebellum**	**R cerebellum**
theta	f: 0.083/0.107	f: 0.030/0.046	f: 0.088/0.167	f: 0.0673/0.1477	f: 0.0670/0.1403	f: 0.050/0.063	f: 0.057/0.119
	s: 0.076/0.088	s: 0.030/0.048	s: 0.089/0.170	s: 0.0674/0.1455	s: 0.0765/0.1777	s: 0.046/0.056	s: 0.056/0.105
alpha	f: 0.062/0.077	f 0.028/0.040	f: 0.084/0.159	f: 0.0742/0.1767	f: 0.0812/0.1977	f: 0.041/0.045	f: 0.047/0.080
	s: 0.073/0.088	s: 0.027/0.037	s: 0.090/0.166	s: 0.0836/0.2052	s: 0.1025/0.2714	s: 0.040/0.040	s: 0.046/0.063
low beta	f: 0.031/0.034	f: 0.013/0.018	f: 0.036/0.064	f: 0.0280/0.0473	f: 0.0296/0.0533	f: 0.015/0.014	f: 0.019/0.025
	s: 0.039/0.040	s: 0.014/0.019	s: 0.040/0.068	s: 0.0344/0.0615	s: 0.0390/0.0754	s: 0.015/0.013	s: 0.020/0.024
high beta	f: 0.018/0.021	f: 0.008/0.012	f: 0.018/0.029	f: 0.0161/0.0285	f: 0.0153/0.0277	f: 0.008/0.008	f: 0.009/0.011
	s: 0.022/0.022	s: 0.008/0.012	s: 0.020/0.031	s: 0.0182/0.0318	s: 0.0189/0.0348	s: 0.008/0.007	s: 0.009/0.010
gamma	f: 0.007/0.006	f: 0.003/0.004	f: 0.006/0.009	f: 0.0064/0.0088	f: 0.0057/0.0088	f: 0.004/0.004	f: 0.005/0.005
	s: 0.007/0.006	s: 0.003/0.003	s: 0.006/0.009	s: 0.0065/0.0090	s: 0.0059/0.0092	s: 0.004/0.004	s: 0.005/0.004

4 Non-Linear Relationship between BOLD Activation and Amplitude of Beta Oscillations in the Supplementary Motor Area during Rhythmic Finger Tapping

Florian Gompf[a], Anja Pflug[a], Helmut Laufs[b], and Christian Alexander Kell[a,*]

[a] Cognitive Neuroscience Group, Brain Imaging Center and Department of Neurology, Goethe University, Frankfurt, Germany

[b] Department of Neurology, University Hospital Schleswig-Holstein, Campus Kiel, Christian-Albrechts-Universitt zu Kiel, Germany

[*] Corresponding author. Tel.: +49-69-6301-6395; E-mail address: c.kell@em.uni-frankfurt.de

Keywords

EEG-fMRI, predictive timing, internal timing, SMA, premotor cortex, beta oscillations

4.1 Abstract

Functional imaging studies using BOLD contrasts have consistently reported activation of the supplementary motor area (SMA) both during motor and internal timing tasks. Opposing findings, however, have been shown for the modulation of beta oscillations in the SMA. While movement suppresses beta oscillations in the SMA, motor and non-motor tasks that rely on internal timing increase the amplitude of beta oscillations in the SMA. These independent observations suggest that the relationship between beta oscillations and BOLD activation is more complex than previously thought. Here we set out to investigate this rapport by examining beta oscillations in the SMA during movement with varying degrees of internal tim-

ing demands. In a simultaneous EEG-fMRI experiment, 20 healthy right-handed subjects performed an auditory-paced finger-tapping task. Internal timing was operationalized by including conditions with taps on every fourth auditory beat, which necessitates generation of a slow internal rhythm, while tapping to every auditory beat reflected simple auditory-motor synchronization. In the SMA, BOLD activity increased and power in both the low and the high beta band decreased expectedly during each condition compared to baseline. Internal timing was associated with a reduced desynchronization of low beta oscillations compared to conditions without internal timing demands. In parallel with this relative beta power increase, internal timing activated the SMA more strongly in terms of BOLD. This documents a task-dependent non-linear relationship between BOLD and beta-oscillations in the SMA. We discuss different roles of beta synchronization and desynchronization in active processing within the same cortical region.

4.2 Introduction

Regular time intervals reflect fundamental characteristics of rhythmic events that the brain uses to optimize perception and motor behavior. Anticipation of future events after having internalized temporal regularities in the sensory input is called internal timing (Nobre et al., 2007) or predictive timing (Arnal and Giraud, 2012). Both cerebral networks that serve rhythm perception and production as well as neural oscillations that serve this function have been identified. Yet, conflicting reports exist regarding the relationship between neural oscillations and BOLD signal associated with internal timing. In this study, we investigated the relationship between neural beta oscillations and activation as measured by BOLD in the cortical core region of rhythm processing, the supplementary motor area (SMA).

Several empirically grounded models propose the SMA, embedded in a cortical and subcortical network, plays a major role in internal time keeping which is a prerequisite for rhythm processing (Schubotz, 2007; Kotz et al., 2009; Large et al., 2015). Neuroimaging studies documented SMA activation for internal time keeping during rhythm perception (Schubotz et al., 2000; Grahn and Brett, 2007; Grahn and Rowe, 2009) and rhythmic finger tapping (Larsson et al., 1996; Jaencke et al., 2000b; Lewis and Miall, 2002; Wiener et al., 2010). Electrophysiological studies focusing on the spectral features of the neural signal of the SMA during rhythm processing identified effects mainly in oscillations in the beta frequency range. In rhythmic finger tapping, rhythmic beta amplitude variations and increased beta coherence between primary motor areas and the SMA have been observed, especially for internally paced tapping (Pollok et al., 2005; Boonstra et al., 2006). Motor beta oscillations may also contribute to auditory rhythm perception even in the absence of overt movement, suggesting an active role in coding temporal predictions (Fujioka et al., 2012, 2015) but see (Meijer et al., 2016)).
On the other hand, the beta rhythm has been considered an idling rhythm in the motor system because beta oscillations increase in synchrony during rest (Pfurtscheller and Lopes da Silva, 1999). Beta rhythms desynchronize before and during a movement and resynchronize after task completion in sensorimotor cortex (Pfurtscheller, 1981; Salmelin et al., 1995; Neuper and Pfurtscheller, 2001). An electrocorticography study documented a similar pattern in the SMA between 18 Hz and 22 Hz (Ohara, 2000). This suggests a negative relationship between the amplitude of beta oscillations and BOLD activation over central regions including the SMA, particularly during motor tasks. Yet, while beta rhythms in sensorimotor cortices are suppressed during movement preparation and execution, beta power increases in motor cortices during anticipation of an upcom-

ing sensory event (Kilavik et al., 2013). Specifically over the SMA, beta power increases have been reported for time estimation in a working memory task between 14 Hz and 30 Hz (Kulashekhar et al., 2016). This beta power increase would argue for a positive relationship between amplitude of beta oscillations and BOLD activation in the SMA.

Together, both beta power decreases and increases have been associated with active processing in the SMA. Task-based EEG-fMRI studies usually reveal relationships between the BOLD signal and EEG power envelope modulations during repeated alternations between a single condition and rest. These studies revealed expectedly a strong negative relationship between beta power and BOLD activation during motor tasks mostly in primary motor cortices but also in the SMA (Formaggio et al., 2008; Ritter et al., 2009; Yuan et al., 2010; Sclocco et al., 2014). Some studies also report positive correlations between the power of beta oscillations and the BOLD signal; however, these findings are far smaller in size and less consistent with regard to the effect location (Ritter et al., 2009; Scheeringa et al., 2009). The relationship between beta oscillations and BOLD activity in the SMA during internal rhythm generation is unclear.

This study addresses these prima vista opposing findings by simultaneously acquiring EEG and fMRI data during a rhythmic finger tapping task. Here we study the relationship between beta power and the BOLD signal beyond movement-related beta desynchronization. Specifically, we investigated internal timing-related effects in the beta band during several tapping conditions with varying demands on internal rhythm generation. In an auditory-paced finger tapping task, participants were either asked to tap on every auditory stimulus (fast tapping rate, F) or on only every fourth identical auditory stimulus (slow tapping rate, S). While the tapping rate changed for slow and fast conditions, the auditory stimulus did not

change across conditions. We hypothesized contrasting the internal generation of a slow rhythm during slow tapping against simple auditory-motor synchronization during fast tapping revealed effects associated with internal timing, because the slow tapping rate was generated internally in the presence of a constant stream of auditory stimuli.

To test for effector effects on SMA activity, tapping was either performed with the left and the right hand. While effects of hand have already been shown for the primary motor areas in electrophysiological and fMRI studies (Jaencke et al., 2000b; Boonstra et al., 2006; Hayashi et al., 2008), effects of hand on beta power in the SMA, however, remain unclear. One could envisage stronger engagement of the SMA during left compared to right hand tapping based on the left-dominant control of both left and right hand unimanual actions with the concomitant increase in interhemispheric information transfer (Schluter et al., 2001; Rushworth et al., 2003).

The study was conducted only in right-handed participants since we were not interested in the effect of left-handedness on brain activity. Also, this study focuses only on beta band power fluctuations because this frequency range has previously been related with internal timing effects(Pollok et al., 2005; Boonstra et al., 2006; Fujioka et al., 2012) even though there is evidence that also alpha and gamma oscillations contribute to explaining variance in the BOLD signal (Scheeringa et al., 2011).

Beta oscillations have been subdivided in relative lower and relative higher frequency ranges. While exact frequency boundaries differ from study to study, low beta oscillations have been associated with long-distance multimodal integration and top-down processing (von Stein, 1999; Kopell et al., 2000; Lee et al., 2013; Bressler and Richter, 2015). High beta oscillations have been observed during movement preparation and sustained movements (Farmer, 1998; Roopun et al.,

2006). Yet, beta oscillations over the SMA have been reported in various frequency ranges (Kaiser et al., 2000; Ohara, 2000; Neuper and Pfurtscheller, 2001; Fujioka et al., 2012). We thus determined low and high beta frequency ranges in our sample and thus analyzed frequency bands from 14 Hz to 24 Hz and 25 Hz to 35 Hz separately. We hypothesized a general beta power decrease across all tapping conditions due to movement generation. Relative increases in beta power in an overall beta-suppressed state, however, should be observed in conditions with higher demands on internal rhythm generation as in slow tapping conditions. At the same time, higher BOLD activity in the SMA should be observed for conditions requiring internal slow rhythm generation. Potentially, the SMA could activate more strongly and beta power could decrease more strongly for left compared to right hand tapping, since left hand tapping requires more interhemispheric information transfer, because unimanual hand control is left-dominant (Schluter et al., 2001; Rushworth et al., 2003).

4.3 Materials and Methods

4.3.1 Participants

Twenty-five participants (10 males; aged 1931 years; mean 23.8 years) were included in the EEG-fMRI study. Participants had normal or corrected-to-normal visual acuity, no neurological deficits and were right-handed according to self-reports and their scores on the Edinburgh inventory of manual preference (mean handedness quotient 85.5, Oldfield (1971)). Participants performed a test run before measurement to become familiar with the task. All participants gave their written informed consent prior to the study and were paid for participation. The study was approved by the local ethics committee of the Medical Faculty of Goethe University Frankfurt (GZ12/14) and is in accordance with the Declaration of

Helsinki.

4.3.2 Auditory-Paced Finger Tapping Paradigm

The paradigm was adapted from Pflug et al. (2017). Using MR-compatible headphones, auditory beats (1.6 kHz, 2 ms duration) were binaurally presented with a constant inter-onset-interval of 400 ms (2.5 Hz, 150 bpm) in all conditions. Participants were asked to tap with their index fingers at a slow or a fast rate synchronized to un-accentuated auditory beats. The fast tapping rate was defined as tapping to every beat. For slow tapping rates, participants were instructed to iteratively count four beats internally and tap only on only every fourth beat. While fast tapping represented simple auditory-motor synchronization, slow tapping required internal generation of a slow rhythm. The auditory stimulus, however, was identical for all conditions. We report here the results of four unimanual conditions that differed in tapping rate/hand mappings (Figure 1). Participants used one hand for tapping the slow or the fast rate while the other hand was not moving (left slow, Sθ; right slow, θS; left fast, Fθ; right fast θF). Please note that there were four additional bimanual conditions during which participants were instructed to tap with both hands the same rate (both fast or both slow) or tapped both rates in parallel (right hand fast and left hand slow rate and vice versa). To reduce complexity, we report here only the unimanual conditions.

Tapping was performed in pseudo-randomized blocks. Tapping blocks lasted 15 s during which 36 auditory beats were presented. This resulted in 36 finger taps in fast conditions and nine finger taps in slow conditions. Before each block, a visual cue indicated the upcoming condition (jittered between 4.6 s and 5.6 s). For each hand, a downward arrow indicated slow tapping, an upward arrow fast tapping, and a dot a stationary hand. Four auditory beats of higher

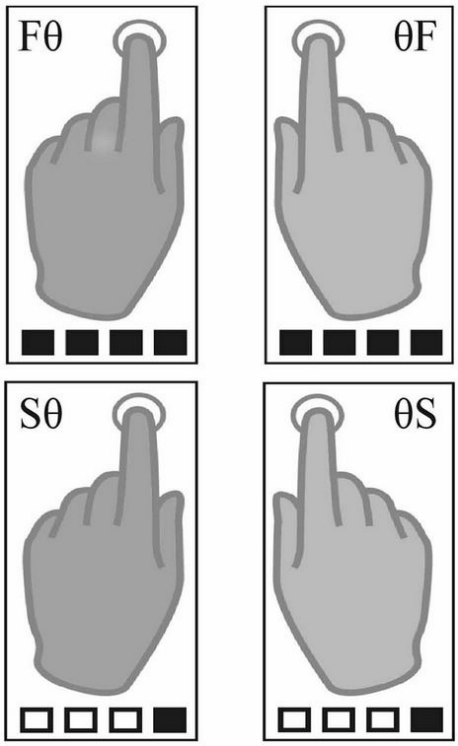

Figure 4.1: Task conditions. The four unimanual conditions included two left-hand (left fast, Fθ; left slow, Sθ) and two right-hand conditions (right fast, θF; right slow, θS). Squares illustrate the auditory beat; black filled squares indicate tapping.

pitch primed the fast tapping rate and tapping onset. An inter-block-interval, during which a fixation-cross was presented, was jittered between 5.5 s and 8 s. All eight conditions were presented six times in randomized order, resulting in a total of 48 blocks lasting 22 min.

4.3.3 Experimental Setup

A projector was used to display the visual stimuli on a screen that participants viewed via an MR compatible mirror and auditory beats were presented using MR-compatible headphones (MRConfon, Magdeburg, Germany). The auditory beats and the visual instruc-

tions were presented with Presentation software (Neurobehavioral Systems, Albany, CA, USA, RRID: SCR002521). Participants were asked to restrict their gaze to the center of the screen during the task. Two pneumatic Biopac pressure sensors (module of model MP150, BIOPAC Systems Inc., Goleta, CA, USA, RRID: SCR014279) were used to record participants tapping pressure. These were attached to the pads of participants index fingers. Participants were lying in a supine position in the MR bore and were asked to tap with their index fingers on their ipsilateral thigh. The pressure sensitivity of the sensors was 0.01 cm H2O with a sampling rate of 1 kHz. Pressure data were inspected for tapping errors. They were below 2(%) in each participant; thus, no participant was excluded from further analyses.

4.3.4 EEG Data Recording and Preprocessing

During scanning, EEG was recorded using a BrainAmp MR EEG amplifier (Brainproducts, Gilching, Germany) and a BrainCap electrode cap (EASYCAP, Herrsching, Germany) with 30 EEG and 2 EOG channels. AgAgCl EEG ring electrodes were positioned according to an extended 10/20 system with a reference electrode placed between Fz and Cz as used in Viola et al. (2009). The impedance of all EEG electrodes was kept below 10 kΩ after preparation. ECG, for cardioballistic artifact correction, and surface EMG, from both extensor digitorum communis muscles, was recorded using an additional BrainAmp ExG MR amplifier with the corresponding EMG connecting device (ExG Aux box). Raw EEG data was sampled at 5 kHz with a range of xxx16.384 mV, a low-pass filter of 250 Hz, and a high-pass filter of 0.1 Hz using the Brain Vision Recorder software. The EEG data recording was synchronized via a SyncBox to the MR scanner clock to improve artifact correction. The entire equipment was MRI compatible and met all security standards

(Brain Products EEG-fMRI Hardware).

EEG off-line artifact correction was performed in Brain Vision Analyzer software (Version 2.1, Brainproducts) according to standard preprocessing procedures (for details see Allen et al. (1998). In brief, gradient artifacts were automatically detected and subsequently subtracted from the data. After down-sampling the data to 250 Hz, R-peaks in the ECG channel were automatically marked and used for correction of cardioballistic artifacts. Before performing an independent component analysis (ICA) to remove additional cardioballistic artifacts, horizontal eye movements and eye blinks, the data were low-pass filtered at 48 Hz and visually inspected for artifacts and manually marked. Marked artifacts were automatically excluded from the subsequent ICA decomposition. A classical sphering approach within an infomax ICA with a convergence bound of 1 101 and a maximum of 512 steps was applied for matrix decomposition. Finally, all channels were referenced to the average of all EEG channels. For each participant, the length of all visually marked artifacts was summed up and set in relation to the total block duration. The entire data set was discarded when more than 10% of the data were affected by artifacts (Laufs et al., 2003). By applying these rules, 5 of the 25 participants were excluded from further analyses.

4.3.5 EEG Power Analysis

To investigate effects of the tapping task on the EEG power spectrum, power spectral density was calculated from the mean signal of EEG electrodes that are sensitive to signal of the SMA (F3, F4, Fz, FC3 and FC4). These electrodes were defined using an independent EEG/MEG measurement in 17 participants from which eight participants also participated in the current EEG/fMRI study. MEG was recorded using a whole-head system (Omega 2005, VSM

MedTech) with 275 channels at a sampling rate of 1200 Hz. Simultaneous EEG was recorded with a custom-made cap equipped with 64 MEG-compatible AG/AgCL electrodes (EASYCAP, Herrsching, Germany). Participants performed the identical finger tapping paradigm during parallel EEG/MEG recording which allows for proper source analyses. MEG and EEG data were filtered off-line with fourth-order Butterworth 300 Hz low-pass and 2 Hz high-pass filters. Line noise at 50 Hz was bandpass-filtered. Recorded data were down-sampled to 1000 Hz. Blocks containing muscle and SQUID artifacts were removed using an automatic artifact rejection algorithm (Oostenveld et al., 2011). Blocks with a head movement exceeding 5 mm were also discarded from further analysis. An ICA was used to identify and reject components of heart muscle and blinks in MEG and EEG data separately. EEG channels were visually inspected and channels containing noise were discarded before EEG signals were re-referenced to a common average. Only valid blocks of both modalities were used for further analysis, which resulted in 815 blocks per condition and subject (mean 12 blocks) for analysis.

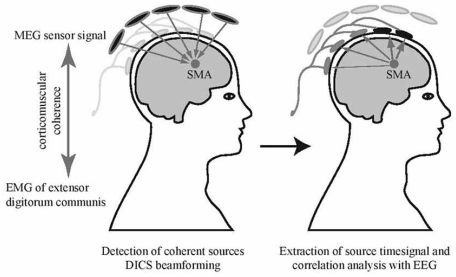

Figure 4.2: Electrode selection. Supplementary motor area (SMA) source signals obtained from MEG beamforming were used for a correlation analysis with simultaneously recorded EEG. Channels with significant correlation were selected (marked in black) and corresponding EEG electrodes in the EEG-fMRI experiment were used for further analyses.

For source identification, the mean activity of the left and the right extensor digitorum communis muscle during the bimanual fast

tapping condition was used as an external reference signal to detect coherent MEG sources in the brain (see Figure 4.2; (Gross et al., 2001; Pollok et al., 2005; Muthuraman et al., 2014). A DICS beamformer (Gross et al., 2001) approach was used to identify sources with highest coherence with the EMG data. The source time series in the SMA were extracted for every condition using the LCMV beamformer method (Van Veen et al., 1997) in a frequency band from 2 Hz to 300 Hz. To detect EEG channels sensitive to the SMA source activity, the correlation between MEG source signal and EEG electrodes was calculated (4.2). To allow for statistical comparisons, surrogate datasets were created with block sequence being randomized for EEG signals but kept constant for MEG source signals. Surrogate values and real correlation values were compared using a paired sample t-test, significance was assumed at $p < 0.05$. This revealed that the EEG electrodes F3, F4, Fz, FC3 and FC4 correlated with activity in the SMA. To assess that signal from close-by cortical sources did not influence signal in the selected electrodes relevantly, we correlated also time courses of both left and right dorsal premotor cortices with the EEG signal. Time courses in these sources did not correlate significantly with activity in the set of SMA-sensitive electrodes (both $p < 0.05$). More detailed results of the MEG data will be presented elsewhere.

Thus, EEG power in a frequency window from 2 Hz to 40 Hz was analyzed in F3, F4, Fz, FC3 and FC4 separately for the conditions and baseline using a multitaper frequency transformation (hanning window). Due to residuals of scanner artifacts in high-frequency ranges (as described in von Wegner et al. (2016)) analyses were restricted to a maximum frequency of 40 Hz. The baseline was defined as the inter-block-interval during which participants were neither tapping, nor instructed for an upcoming tapping block. Mean power across electrodes was plotted over frequencies, separately for each

condition and baseline. Peaks in the theta and alpha range included harmonics of the auditory stimulation rate at 2.5 Hz and were thus not further analyzed. Power spectra revealed expectedly two beta components: low beta peaked between 19 Hz and 20 Hz and high beta between 29 Hz and 30 Hz with a trough at 25 Hz between them. These peaks did not correspond to harmonics of 2.5 Hz oscillations or of multiples of the scanning sequences repetition time of 2.08 s. We thus further studied power in the low and high beta band separately in frequency windows between 14 Hz and 24 Hz and 25 Hz and 35 Hz.

First, all tapping conditions were compared with fixation baseline using paired t-tests ($p < 0.05$, Bonferroni corrected for multiple comparisons which results in a significance level of $p < 0.0125$) separately for mean power differences in low (14 - 24 Hz) respective high (25 - 35 Hz) beta. Second, condition differences were investigated using a 2 2 ANOVA with timing (internal slow rhythm generation, auditory-motor synchronization) and hand (left, right) as factors. Post hoc t-tests were additionally performed for significant main effects ($p < 0.05$, Bonferroni corrected for multiple comparisons). All analyses were performed in SPSS for low and high beta separately (IBM SPSS Statistics).

4.3.6 fMRI Recording and Preprocessing

Image acquisition was performed on a Siemens Trio 3 Tesla magnetic resonance system (Siemens MAGNETOM Vision, Erlangen, Germany) equipped with a circular polarized Send/ Receive head coil with an integrated preamplifier. Functional images were obtained with a gradient-echo T2-weighted transverse echo-planar imaging sequence (614 volumes; repetition time (TR) = 2.08 s; echo time (TE) = 29 ms; flip angle = 90°; 32 axial slices in descending order; 3 mm 3 mm 3 mm isotropic voxel size). Additionally, high-resolution T1-

weighted anatomical scans (TR = 2.25 s; TE = 3.83 ms; flip angle = 9°; 176 slices per slab; 1 mm3 isotropic size) were obtained. To reduce head motion, a vacuum cushion was used (Vac Fix System, Avondale, AZ, USA).

Image processing and data analyses were performed in SPM12 (Welcome Trust Centre for Neuroimaging, London, UK). After eliminating the first four volumes in each participant due to field inhomogeneity of the scanner in the beginning of each run, standard preprocessing was performed (realignment, co-registration of anatomical T1-images to the mean functional image with subsequent segmentation using Tissue Probability Maps, normalization to the Montreal Neurological Institute (MNI) standard brain template, and smoothing with an 8 mm full-width at half-maximum Gaussian kernel). The preprocessed images were analyzed within the framework of general linear models (GLM) for time-series data (Worsley and Friston, 1995).

4.3.7 fMRI Region of Interest Analysis in the SMA

To investigate condition-related BOLD effects associated with internal timing in the SMA, a fMRI region of interest analysis was performed. On the single-subject level, four condition-specific regressors of interest (for Sθ, θS, Fθ, θF) in addition to four regressors of no interest (bimanual conditions) were modeled by convoluting the onsets and durations of conditions (modeled by boxcar functions) with the canonical hemodynamic response function to obtain predicted BOLD responses. Additional nine regressors of no interest were capturing the variance associated with the instructions for each conditions and an additional tap participants usually made after the last metronome click in fast conditions. Six non-convolved regressors were modeling head-motion-related effects.

For group-level analyses, the four regressors of interest, modeling

condition-specific tapping effects, were included in a 2 2 ANOVA, similar to the aforementioned EEG analysis. The SMA coordinate %(0/0/70, x/y/z, MNI space) reflected the MNI coordinate of the MEG source (see above). Because the coordinate falls in the inter-hemispheric fissure, two cubic ROIs were used to extract fMRI beta values from the left and right SMA, separately (left SMA: -100/-100/6070, min.max. x/min.max. y/min.max. z, MNI space and right SMA: 010/-100/6070, min.max. x/min.max. y/min.max. z, MNI space). For each of the four conditions of interest, average beta values for the two ROIs were extracted from all 20 subjects with their respective standard error of the mean (MarsBaR region of interest toolbox for SPM, RRID: SCR009605). Analyses were performed for the left and right SMA separately in SPSS ($p < 0.05$, IBM SPSS Statistics, RRID: SCR002865).

4.4 Results

4.4.1 EEG Power Analysis

The condition-specific power spectral density between 15 Hz and 40 Hz in electrodes over the SMA is depicted in Figure 4.3. For low and high beta, all tapping conditions showed a reduction in power compared to baseline (all $p < 0.007$, corrected for multiple comparisons, Figure 4.3A). More importantly, the ANOVA revealed a main effect of timing in the low beta band ($p = 0.023$, $F = 6.163$, Figures 4.3A,B) while for the high beta band no effect of timing was found ($p = 0.343$, $F = 0.946$). Post hoc t-tests in the low beta band revealed higher low beta power in slow than in fast tapping conditions ($p = 0.031$, corrected for multiple comparisons, Figure 4.3B). Conversely, a main effect of hand was found for the high beta band ($p = 0.034$, $F = 5.228$, Figures 4.3A,C) but not in the low beta band ($p = 0.156$, $F = 2.184$). In the high beta band, post hoc t-tests revealed stronger power decreases for the left than for the

right hand ($p = 0.031$, corrected for multiple comparisons, Figure 4.3C). No interactions between timing and hand were foundneither in the low nor in the high beta band (all $p < 0.05$). Yet, the hand effect resulted primarily from the F0 condition, which showed the strongest high beta power decrease (Figure 4.3A).

4.4.2 fMRI Activation

To investigate BOLD signal condition differences in the SMA, ROI analyses were performed. As expected, all conditions showed more activation compared to fixation baseline (Figures 4.4A,B). A main effect of timing was found in the ANOVA, both for the left and right SMA (left SMA: $p = 0.003$, $F = 11.188$; right SMA: $p = 0.004$, $F = 10.917$; Figures 4.4C,D). Post hoc t-tests revealed stronger activation for internal slow rhythm generation than for auditory-motor synchronization in both the left and right SMA (left SMA: $p = 0.003$, corrected for multiple comparisons; right SMA: $p = 0.004$, corrected for multiple comparisons, Figures 4.4A,B). Neither the left nor the right SMA showed a significant main effect of hand or significant interactions between hand and timing (all $p < 0.05$).

4.5 Discussion

Our study revealed four key findings in the SMA. First, the comparisons against baseline revealed the well-known condition-independent task-related desynchronization of low and high beta oscillations together with a concomitant BOLD activation. Second, within the overall suppressed beta state of the SMA during tapping, generation of an internal rhythm relatively increased beta amplitude in parallel to a concordant increase in BOLD activation. Third, and as a consequence of finding one and two, no general linear relationship between the EEG signal in the beta band and the BOLD signal was found. Fourth, tapping with the left compared to right hand de-

creased beta power in the SMA, particularly for fast tapping, while this effect was not observed in BOLD.

When investigating SMA activity-sensitive EEG electrodes for condition effects in relation to baseline, beta desynchronization was found for all conditions in the low (1424 Hz) and high beta band (2535 Hz). Since these effects were condition-independent they likely relate to a general task-related activation of the SMA. Indeed, BOLD analyses documented such activation that has previously been related to movement effects in fMRI finger tapping studies (Rao et al., 1993; Jaencke et al., 2000a; Meister et al., 2005; Witt et al., 2008). The negative relationship between beta power and BOLD signal increase in the SMA and other motor-related cortices is known for motor tasks, but has also been documented in the inferior frontal gyrus and parietal cortices (Formaggio et al., 2008; Ritter et al., 2009; Yuan et al., 2010). It is thus likely that movement planning, anticipation, or execution decreases beta power and increases BOLD activity in the SMA.

The second key finding breaks the inverse relationship between beta power and BOLD activation in the SMA. Internal timing increased, both, beta power and fMRI activation of the SMA in comparison to conditions with low internal timing demands. The increase of activation is in line with findings in which SMA activation has been associated with internal time keeping (for review see Grahn and Rowe (2009); Wiener et al. (2010). EEG effects associated with internal timing were only observed in the low beta band in our study. This specifies previous proposals on the contribution of beta oscillations to predictive timing (Schubotz, 2007; Arnal and Giraud, 2012; Bartolo et al., 2014; Bartolo and Merchant, 2015; Kulashekhar et al., 2016; Morillon et al., 2016). Beta oscillations in sensorimotor cortex increase in power in anticipation of future events whenever temporal predictions are possible (Kilavik et al., 2013). This sug-

gests that beta oscillations may serve as a timing mechanism not only in rhythmic conditions but rather serve as an internal clock to predict timing of future events even when they do not occur rhythmically. Rhythmic signals from the motor cortex could reset timers in sensory cortices to improve temporal predictions of future sensory events (Fujioka et al., 2012; Morillon et al., 2014, 2015). Information passing between brain regions in large scale neural networks including motor cortices cycles in beta frequencies, suggesting that the motor system receives and/or transmits information to other brain regions in beta-long segments (Picazio et al., 2014). Indeed, motor cortices form large scale neural networks with distant cortical regions by means of beta synchronization (Roelfsema et al., 1997; Gehrig et al., 2012; Bressler and Richter, 2015).

The opposing observation of parallel movement-related beta desynchronization and internal timing-related beta synchronization in the same activated cortical region could be explained if both power modulations (in comparison to baseline and in comparison to the movement-related suppression without internal timing demands) were interpreted as active processes. A recent neurodynamic model focusing on cortico-hippocampal interactions during memory encoding proposes an innovative perspective on the active role of beta desynchronization even in non-motor cortices (Hanslmayr et al., 2016). Neocortical alpha and beta desynchronization may interact with theta-gamma synchronization in the hippocampus, which results in long-term potentiation and memory formation. This model proposes an increase in information processing, as measured by neuronal firing rates, with neocortical beta power decrease. The baseline in our experiment, which required no movement, could be regarded as a perfectly predictable condition during which beta oscillations in motor cortices idle because no computations are required. Activation of a given cortical region could potentially result in beta

synchronization in local neural ensembles that are out of phase of neighboring patches within a given cortical region. This would in turn appear as a strong desynchronization when measuring the entire cortical region on the mesoscopic level. If indeed beta oscillations in the motor-related cortices carry time information then this information would likely be used by many neural ensembles within a given region and would additionally be disseminated to other cortical regions. This would result in the here observed beta power increases for conditions requiring additional internal timing that were embedded in an overall movement-related beta suppression. Interestingly, the timing effects were found consistently only in the low beta band, while both beta bands were suppressed in every condition compared to baseline. This suggests that particularly the low beta band carries temporal information and could be used for predictive timing (Kopell et al., 2000; Lee et al., 2013).

Earlier studies associated the simultaneous occurrence of cortical synchronization and desynchronization in alpha and low beta bands with processing in thalamo-cortical networks (Pfurtscheller and Lopes da Silva, 1999). Subcortical brain regions contribute substantially to rhythm processing, as evidenced by lesion studies or observations in Parkinsons disease patients and interactions between the SMA, the basal ganglia, and the cerebellum are thought to underlie efficient control of rhythmic movements (Riecker et al., 2005; Schwartze et al., 2012).

The diminished beta band desynchronization for slow compared to fast finger tapping could potentially also be interpreted as a consequence of different tapping rates. Yet, if reduced motor activity in slow compared to fast tapping would relate to the observed beta power increase, consequences of rate effects would also apply to the fMRI results. Higher tapping rates are linearly related with BOLD increases, however, in primary motor cortices (Hayashi et al., 2008).

The current fMRI BOLD analysis revealed the opposite effect in the SMA: less instead of more activation for fast conditions. This excludes tapping-rate effects.

While effects of internal timing were observed in the low beta band, effects of hand were limited to the high beta band. This is not only in accordance to previous findings, which associate finger movement to oscillations in the high beta band in the SMA (Pfurtscheller et al., 2003), but also extends these findings by showing stronger high-beta desynchronization for the non-dominant left hand in right-handed participants. This observation could be explained by the need for additional interhemispheric information transfer and thus increased processing demands in the SMA in left hand tapping, because unimanual hand motor control seems to be left-dominant (Schluter et al., 2001; Rushworth et al., 2003). The non-dominant left hand is less frequently used for finger tapping. Consequently, left hand tapping could be regarded as more difficult. Indeed, previous electrophysiological findings in tapping and working memory tasks showed stronger beta desynchronization for increasing task difficulty (Mayville et al., 2001; Lundqvist et al., 2011). Of note, the hand effect was only observed in the high beta band and not in BOLD data, which again suggests that not all beta effects translate equally into changes in BOLD activation.

Our results indicate that beta suppression cannot be simply equated with increases in BOLD signal. While the relationship between beta power and BOLD activation may differ from brain region to brain region (Kujala et al., 2014), we show here that even within a single cortical region, contextual task effects change the correlation between beta power and BOLD activity. Since effects of movement-related beta desynchronization and of internal timing-related beta synchronization occurred in parallel in our experiment, both effects could influence the relationship between beta oscillations and

BOLD at the same time. This documents non-linear relationships between the BOLD signal and beta oscillations within the SMA for a timing-related finger-tapping task and questions over-simplified associations between neural oscillations and the BOLD signal.

4.5.1 Limitations

Internal timing-related effects have mostly been associated with oscillations in the beta band (Gerloff and Andres, 2002; Pollok et al., 2005; Boonstra et al., 2006; Fujioka et al., 2012); thus, this study addresses the relationship between beta band power fluctuations and BOLD. However, investigations in other frequency bands as alpha or gamma would also be of interest since alpha and gamma oscillations also contribute to explaining BOLD variance (Scheeringa et al., 2011). It would also be of interest to investigate movements with a wider range of internal timing demands. A parametric design using lower and higher-order tapping rates, representing different levels of internal-timing demands, could be used to further quantify the observed timing effect.

Our study design included eight conditions and was thus not ideally designed for classical EEG-fMRI analyses of correlations between the BOLD signal and EEG power fluctuations over time, especially with respect to analyses of correlations between the beta power envelope beyond task-related desynchronizations with BOLD activity. Such an analysis requires larger time windows for correlation compared to the block length used in this study. With the knowledge of internal timing-related effects for unimanual conditions, a reduced task design with only unimanual conditions and longer tapping blocks could be more appropriate to capture such effects using standard analyses.

The EEG electrode selection was based on significant correlation with MEG source signal in the SMA. We are thus confident that

the signal reflects activity in the SMA. Yet, we cannot exclude that these electrodes also picked up signal from neighboring cortices like slightly more lateral aspects of the dorsal premotor cortex. We believe their contribution is marginal since time courses in the left and right dorsal premotor cortices did not correlate with the set of EEG electrodes reflecting activity in the SMA.

4.6 Conclusion

In conclusion, our findings suggest internal timing-related low beta synchronization occurs in the context of movement-related beta desynchronization in the SMA. The non-linear relationship between beta power effects and BOLD activation is suggestive of active contributions of both regional beta desynchronization and subregional beta synchronization to active processing.

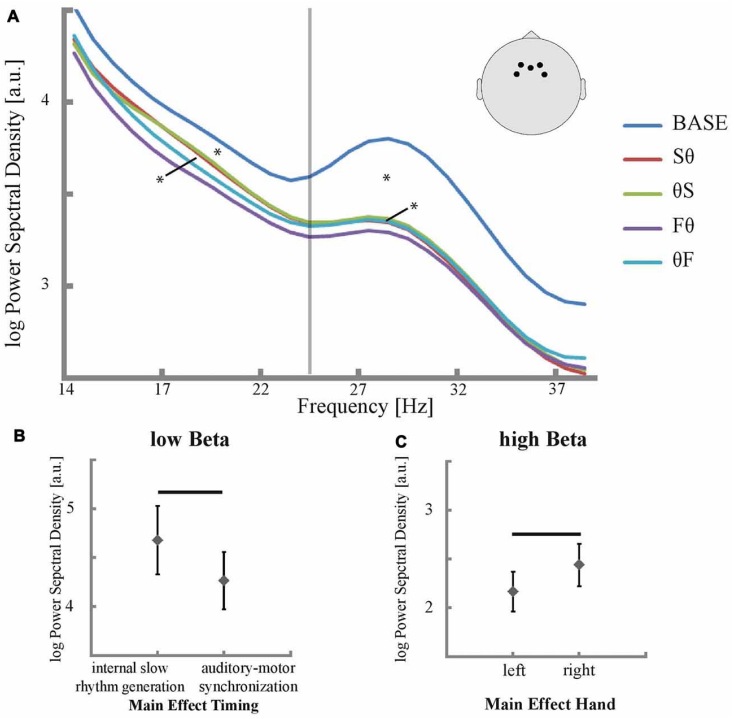

Figure 4.3: Power in EEG electrodes that are sensitive to activity in the SMA and their significant main effects. (A) Mean power spectral density was plotted between 14 Hz and 40 Hz for all conditions and baseline. Significant differences in low and high beta power of conditions compared to baseline are marked with an asterisk ($p < 0.05$, corrected for multiple comparisons) as well as significant main effects of time in low beta power and of hand in high beta power ($p < 0.05$). The positions of the selected electrodes F3, F4, Fz, FC3 and FC4 are illustrated. The vertical line indicates the trough in the power spectrum between low and high beta at 25 Hz. (B,C) Main effect of timing respective main effect of hand for low respective high beta power ($p < 0.05$). Significant differences between internal slow rhythm generation (Sθ and θS) and auditory motor synchronization (Fθ and θF) as well as differences between left and right hand are marked with a black bar ($p < 0.05$, corrected for multiple comparisons).

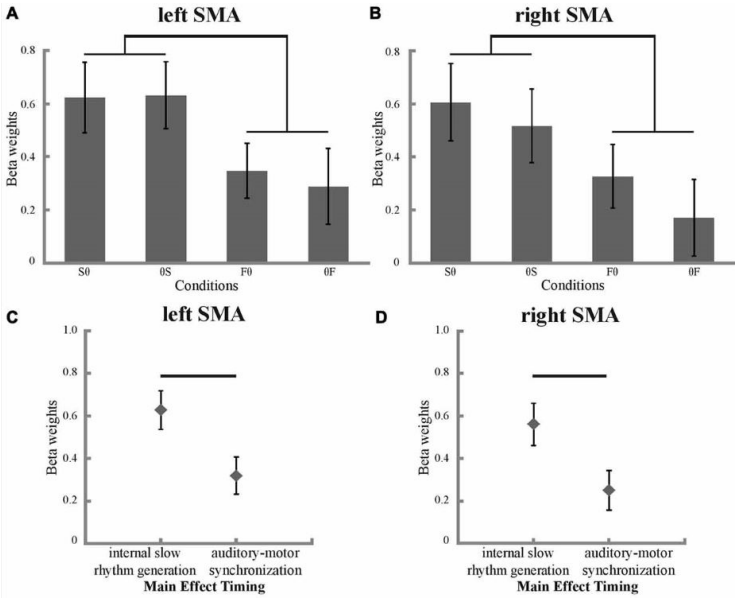

Figure 4.4: Beta weights and their significant main effect of timing in the SMA. Condition-specific beta weights are plotted separately for the left (A) and right (B) SMA. Significant differences between internal slow rhythm generation (Sθ and θS) and auditory motor synchronization (Fθ and θF) are marked with a black bracket ($p < 0.05$, corrected for multiple comparisons). Main effect of timing in the left (C) and right (D) SMA ($p < 0.05$). Significant differences between internal slow rhythm generation (Sθ and θS) and auditory motor synchronization (Fθ and θF) are marked with a black bar ($p < 0.05$, corrected for multiple comparisons).

5 General discussion

The main statement of the DFF theory is, that there exists a mechanism in the brain which splits frequency features of a multifrequent sensory stimulus into two representations which are then processed differently by the two cerebral hemispheres. While the left hemisphere preferably processes high frequencies, the right hemisphere preferably processes low frequencies of the stimulus. The main goal of this thesis was to investigate whether this theory explaining hemispheric preferences for relative frequencies in the sensory domain is generic enough to be translated to the motor domain. The short answer is, it depends. In the following section, I am going to fuse the results of the last three chapters to describe the mechanisms found in our finger tapping paradigm and how they are related to the proposals of the DFF theory.

5.1 Hemispheric preferences are observed when tapping syncopated rhythms

When assuming hemispheric preferences for motor control we expected to find effects of these preferences in behavioral changes. Here we investigated timing accuracy and accentuation pattern via finger tapping on a pressure sensor. We expected to find a right hand benefit in fast and a left hand benefit in slow tapping. While a right hand benefit for timing accuracy when tapping fast is known (Peters, 1980; Ivry, 1996), a left hand benefit for slow tapping was only found under specific experimental settings. In our finger tapping paradigm, we detected a left hand benefit for slow tapping only when using a syncopated rhythm (Pflug et al., 2017). That this finding is in line with the DFF theory will become clear when looking at the stimuli used by Ivry and colleges. When the authors of the DFF theory found hemispheric preferences in stroke patients, they used

multifrequent visual stimuli. Those stimuli included features with high and low frequency components (see figure 1.2). On the perceptual level they induced two percepts which cannot be integrated (e.g you can either see the ants or the anthill). Comparing an integrated meter (standard quadruple meter) with a more complex, not integrated meter (syncopated), we showed that an earlier integration (culturally learned) of rhythms weakens hemispheric preferences for relative frequencies. This suggests that over-learned poly-rhythms may be represented as an integrated Gestalt potentially within a hemisphere, while syncopated poly-rhythms may be represented in a more segregated way over hemispheres.

Storage of known sequences is a key feature of the left hemisphere and becomes visible in left hemispheric stroke patients, who can no longer reproduce learned motor sequences (Dovern et al., 2016; Haaland and Harrington, 1994). We showed that the standard quadruple meter in our participants canceled the left hand benefit in slow tapping, suggesting that this rhythm is a known sequence which might be stored in the left hemisphere. In line with these findings, when participants tapped a syncopated meter a small but consistent effect occurred – a left hand benefit for slow tapping. This suggests a more dominant role of the right hemisphere when tapping a syncopated rhythm and could indicate a parallel processing of the two rhythms by the two cerebral hemispheres. Using syncopated rhythms in perceptual tasks lead to a higher activation of the right hemisphere in non-musicians, indicating a parallel processing, while there is a shift to the left hemisphere for musicians (Vuust et al., 2005), suggesting an integration via learning.

Other behavioral results in our study also supported the splitting theory in syncopated rhythms. While in the syncopated tapping paradigm participants accentuated every fast tap in the multi-frequent conditions, only the first, metric tap was stronger when tapping the

standard quadruple meter. The pronounced accentuation in the syncopated paradigm is related to a higher amount of attention which is typical for non-integrated rhythms (Nozaradan et al., 2012). Beats integrated in a meter can be processed with lower attention on single beat positions (London, 2012; Povel and Essens, 1985; Rhodes et al., 2004). Non-integrated rhythms are harder to perform and every participant who performed both paradigms confirmed that they had to focus more in the syncopated tapping and were not able to stop focusing, otherwise they lost the meter. When comparing confusions in multi-frequent tapping conditions, participants tapping the syncopated rhythm made more errors compared to participants tapping the standard quadruple meter (see Table 2.1). Additionally, more errors were found when hemispheric preferences were violated. All behavioral results indicate that a syncopated tapping paradigm reveals hemispheric preferences for relative frequencies as proposed by the DFF-theory. This effect must have a correlate in the neural data.

5.2 The roles of the auditory association cortices in rhythm processing

Neural data was recorded using the syncopated tapping paradigm. In the next sections, the differences of the two monofrequent conditions are discussed. For fast > slow tapping the fMRI activity increased in the primary motor cortices as expected. In these areas fast tapping leads to a decrease in the low beta band activity which is known in the literature as beta-desynchronization (Pfurtscheller et al., 2003). Since in both conditions auditory cues were used for the pacing of the fast rhythm, no cortical structures known to be involved in external timing (e.g. dPMC) were activated. When comparing the activation of slow > fast tapping, our assumptions of a parallel processing between the hemispheres for the two tap-

ping rhythms were confirmed. A right hemispheric activation when participants had to generate a slower internal rhythm on top of the paced fast one was found. Only the auditory association cortex was right-lateralized.

In the MEG, we focused on the low-beta band which has been related to internal timing (Gompf et al., 2017; Fujioka et al., 2012). The SMA, as well as the cerebellum and the primary motor cortices, represented the actual tapped rhythms in a low-beta power modulation. Because of the bimanual motor output, there was no lateralization found in these areas. However, the auditory association cortices showed hemispheric differences when participants were tapping the slow rhythm. While the right auditory cortex clearly represented the slow, internal generated rhythm similar to the representation in the SMA, the left auditory association cortex showed patterns of both rhythm with a strong additional representation of the fast beat. In the slow tapping condition, in which we assumed a frequency splitting between the hemispheres, the frequency representation of the slow rhythm was higher in the right auditory association cortex and the frequency representation of the fast rhythm was higher in the left auditory cortex. Our findings identify a sensory source as basis of the lateralization process expressed in the behavioral data. This observation fits to the proposals of the sensory-driven hypothesis on hemispheric specialization (Minagawa-Kawai et al., 2011; Ivry and Robertson, 1998). When investigating single trial beta power modulations we could show that in the right but not in the left auditory association cortex amplitude modulation was related with performance. For fast trials the only difference between too long and too short intervals was found in the SMA where beta-power was higher for too long intervals. This indicates that there are two separate mechanisms for short and long interval timing (Morillon et al., 2009) – with short intervals coded in the motor system and

left auditory association cortex (with the help of the cerebellum) and long intervals in the right auditory cortices.

5.3 Communication between the SMA and the auditory cortices is used for rhythm integration

In the connectivity analysis between the SMA and both auditory cortices we saw that both auditory association cortices connect to the SMA during slow rhythm generation. Since the left auditory association cortex represented the faster rhythm more strongly and the right auditory association cortex represented the slower rhythm more strongly, we interpreted this as frequency specific information passing to the SMA. The SMA is known to be important in rhythm processing (Schubotz, 2007; Kotz et al., 2009; Large et al., 2015) and bimanual coordination (Gerloff and Andres, 2002; Jaencke et al., 2000b). The SMA therefore integrates rhythms. Another connection was found from the SMA to the left auditory cortex. This suggests that bidirectional auditory-motor interactions help strengthening rhythm integration in hierarchical loops. If our assumption is valid and the SMA receives input from the auditory cortex for rhythm integration, then the communication from the right auditory cortex to the SMA is only necessary in cases where rhythms are not yet integrated, otherwise integrated information can be processed in the left hemisphere. We therefore conducted another fMRI recording (not included in the earlier chapters, unpublished results), where participants tapped the standard quadruple meter (n=12). Connectivity was calculated between the right and left SMA, and right and left auditory cortex using psychophysiological interaction (PPI). Results of the PPI indicate that connectivity for bimanual slow compared to bimanual fast tapping between right SMA and rA2 was higher in the subjects tapping the syncopated rhythm than for subjects tapping the standard quadruple meter. This shows that

in the non-syncopated tapping paradigm the impact of the right hemisphere is reduced and confirms additionally our hypothesis of hemispheric preferences for non-overlearned sequences.

5.4 The role of the low beta band in internal timing and rhythm integration

Investigation of the electrophysiological data has shown that differences between slow and fast tapping were strongest in the low beta band. This was true in the MEG as well as in the EEG data which was recorded in parallel to the fMRI. The investigation of the relation between BOLD and electrophysiological recordings is still in its baby-shoes. Scheeringa et al. (2011) showed that "BOLD signal in humans performing a cognitive task is related to neuronal synchronization across different frequency bands" while BOLD being increased with higher gamma and decreased with higher alpha and beta power. This suggests different relations between higher and lower frequency bands of neural population activity and active processing in this region. In motor cortices, movement leads to beta de-synchronization and gamma power increases concomitant with an increase of BOLD activity (Kilavik et al., 2013). However, in our study low beta power increases were directly coupled with an increase in BOLD in the SMA when comparing slow and fast tapping. This is in contrast to the relation in the beta de-synchronization during fast tapping where a higher BOLD was correlated with lower beta power. This points to a role of beta power increases in internal timing compared to the more prominent beta suppression during motor planning and execution (Pfurtscheller, 1981). Recent studies pointed to this role of beta (Fujioka et al., 2015; Kononowicz and Rijn, 2015). Oscillations in beta band couple distant brain regions for long range communication within the brain (Roelfsema et al., 1997; Gehrig et al., 2012; Bressler and Richter, 2015) and

invasive studies have shown that they are used in subcortical areas like thalamus and basal ganglia to code for beginning and endings of sequences (Herrojo Ruiz et al., 2014a,b). To better understand the relation between BOLD and EEG, our next step is to investigate into the invasive recordings where we also recorded EEG in combination with sEEG or EcoG. These measures should enable us to have a closer look at activation in the gamma range. We expect to find higher gamma in slow compared to fast tapping in the SMA which could explain higher BOLD in this contrast.

5.5 Implementation for clinical purposes

We showed that there seems to be a shift from bi-hemispheric activation during learning to a combined representation in one hemisphere after successful integration driven by sensory areas. This finding could be used to improve clinical cases for patients who are unable to learn new motor sequences like in left hemispheric stroke patients. In some of these cases it is possible that not the sequences per see are destroyed but the access to them. It has been shown that neural coupling with the SMA is reduced in stroke patients compared with healthy controls (Wang et al., 2011). We showed that the SMA connectivity from the right auditory cortex is increased when learning new sequences and that the result of the integration is transferred to the left hemisphere. Using multifrequent movements should strengthen these connections and might help to re-access "lost" sequences. In left hemispheric stroke patients where the right hemisphere has an extended ability to disturb the sequence creation, musical training with multi-frequent rhythms could help to re-implement the ability of the left hemisphere in sequence learning (Lim et al., 2013; Thaut and McIntosh, 2014). Our findings give a good argument why musical therapy is useful.

6 General Conclusion

This thesis was used to investigate whether the double-filtering-by-frequency (DFF) theory could be transferred from the sensory domain into the motor domain. Our results provide empirical evidence for frequency-dependent lateralization in the motor domain and show that hemispheric preferences are driven by the sensory cortices.

References

Aboitiz, F. and Montiel, J. (2003). One hundred million years of Interhemispheric communication: the history of the corpus callosum. *Brazilian Journal of Medical and Biological Research*, 36:409–420.

Albouy, P., Weiss, A., Baillet, S., and Zatorre, R. J. (2017). Selective Entrainment of Theta Oscillations in the Dorsal Stream Causally Enhances Auditory Working Memory Performance. *Neuron*, 94(1):193–206.e5.

Allen, P. J., Polizzi, G., Krakow, K., Fish, D. R., and Lemieux, L. (1998). Identification of EEG Events in the MR Scanner: The Problem of Pulse Artifact and a Method for Its Subtraction. *NeuroImage*, 8(3):229–239.

Alm, P. A. (2004). Stuttering and the basal ganglia circuits: a critical review of possible relations. *Journal of Communication Disorders*, 37(4):325–369.

Andres, F. G., Mima, T., Schulman, A. E., Dichgans, J., Hallett, M., and Gerloff, C. (1999). Functional coupling of human cortical sensorimotor areas during bimanual skill acquisition. *Brain*, 122(5):855–870.

Ansari, D. (2008). Effects of development and enculturation on number representation in the brain. *Nature Reviews. Neuroscience*, 9(4):278–291.

Arnal, L. H. and Giraud, A.-L. (2012). Cortical oscillations and sensory predictions. *Trends in Cognitive Sciences*, 16(7):390–398.

Assaneo, M. F. and Poeppel, D. (2018). The coupling between auditory and motor cortices is rate-restricted: Evidence for an intrinsic speech-motor rhythm. *Science Advances*, 4(2):eaao3842.

Bartolo, R. and Merchant, H. (2015). Oscillations Are Linked to the Initiation of Sensory-Cued Movement Sequences and the Internal Guidance of Regular Tapping in the Monkey. *Journal of Neuroscience*, 35(11):4635–4640.

Bartolo, R., Prado, L., and Merchant, H. (2014). Information Processing in the Primate Basal Ganglia during Sensory-Guided and Internally Driven Rhythmic Tapping. *Journal of Neuroscience*, 34(11):3910–3923.

Bastos, A. M., Vezoli, J., Bosman, C. A., Schoffelen, J.-M., Oostenveld, R., Dowdall, J. R., De Weerd, P., Kennedy, H., and Fries, P. (2015). Visual Areas Exert Feedforward and Feedback Influences through Distinct Frequency Channels. *Neuron*, 85(2):390–401.

Behroozmand, R., Ibrahim, N., Korzyukov, O., Robin, D. A., and Larson, C. R. (2015). Functional role of delta and theta band oscillations for auditory feedback processing during vocal pitch motor control. *Frontiers in Neuroscience*, 9:10.3389/fnins.2015.00109.

Berker, E. A., Berker, A. H., and Smith, A. (1986). Translation of Broca's 1865 report. Localization of speech in the third left frontal convolution. *Archives of Neurology*, 43(10):1065–1072.

Berlin, C. I., Lowe-Bell, S. S., Cullen, J. K., and Thompson, C. L. (1973). Dichotic speech perception: an interpretation of right-ear advantage and temporal offset effects. *The Journal of the Acoustical Society of America*, 53(3):699–709.

Blinowska, K. J. (2011). Review of the methods of determination of directed connectivity from multichannel data. *Medical & Biological Engineering & Computing*, 49(5):521–529.

Boemio, A., Fromm, S., Braun, A., and Poeppel, D. (2005). Hierarchical and asymmetric temporal sensitivity in human auditory cortices. *Nature Neuroscience*, 8(3):389–395.

Boonstra, T., Daffertshofer, A., Peper, C., and Beek, P. (2006). Amplitude and phase dynamics associated with acoustically paced finger tapping. *Brain Research*, 1109(1):60–69.

Branch, C., Milner, B., and Rasmussen, T. (1964). INTRACAROTID SODIUM AMYTAL FOR THE LATERALIZATION OF CEREBRAL SPEECH DOMINANCE; OBSERVATIONS IN 123 PATIENTS. *Journal of Neurosurgery*, 21:399–405.

Bregman, A. S. (1994). *Auditory Scene Analysis: The Perceptual Organization of Sound*. MIT Press.

Bressler, S. L. and Richter, C. G. (2015). Interareal oscillatory synchronization in top-down neocortical processing. *Current Opinion in Neurobiology*, 31:62–66.

Chang, S.-E. and Zhu, D. C. (2013). Neural network connectivity differences in children who stutter. *Brain: A Journal of Neurology*, 136(Pt 12):3709–3726.

Chen, J. L., Zatorre, R. J., and Penhune, V. B. (2006). Interactions between auditory and dorsal premotor cortex during synchronization to musical rhythms. *NeuroImage*, 32(4):1771–1781.

Cooper, G. and Meyer, L. B. (1963). *The Rhythmic Structure of Music*. University of Chicago Press.

Corballis, M. C. (2014). Left Brain, Right Brain: Facts and Fantasies. *PLoS Biology*, 12(1).

Crowe, D. A., Zarco, W., Bartolo, R., and Merchant, H. (2014). Dynamic Representation of the Temporal and Sequential Structure of Rhythmic Movements in the Primate Medial Premotor Cortex. *Journal of Neuroscience*, 34(36):11972–11983.

de Guise, E., del Pesce, M., Foschi, N., Quattrini, A., Papo, I., and Lassonde, M. (1999). Callosal and cortical contribution to procedural learning. *Brain*, 122(6):1049–1062.

Delis, D. C., Robertson, L. C., and Efron, R. (1986). Hemispheric specialization of memory for visual hierarchical stimuli. *Neuropsychologia*, 24(2):205–214.

Delorme, A., Rousselet, G. A., Mac, M. J.-M., and Fabre-Thorpe, M. (2004). Interaction of top-down and bottom-up processing in the fast visual analysis of natural scenes. *Brain Research. Cognitive Brain Research*, 19(2):103–113.

Doelling, K. B. and Poeppel, D. (2015). Cortical entrainment to music and its modulation by expertise. *Proceedings of the National Academy of Sciences of the United States of America*, 112(45):E6233–6242.

Dong, Z.-Y., Liu, D.-Q., Wang, J., Qing, Z., Zang, Z.-X., Yan, C.-G., and Zang, Y.-F. (2012). Low-frequency fluctuation in continuous real-time feedback of finger force: a new paradigm for sustained attention. *Neuroscience Bulletin*, 28(4):456–467.

Dovern, A., Fink, G. R., Timpert, D. C., Saliger, J., Karbe, H., Weiss, P. H., and Koch, I. (2016). Timing Matters? Learning of Complex Spatiotemporal Sequences in Left-hemisphere Stroke Patients. *Journal of Cognitive Neuroscience*, 28(2):223–236.

Dowling, W. J. (2014). *Psychology and Music: The Understanding of Melody and Rhythm*. Psychology Press.

Drake, C. and Palmer, C. (1993). Accent structures in music performance. *Music Perception: An Interdisciplinary Journal*, 10(3):343–378.

Drake, C. and Palmer, C. (2000). Skill acquisition in music performance: relations between planning and temporal control. *Cognition*, 74(1):1–32.

Engel, A. K. and Fries, P. (2010). Beta-band oscillations–signalling the status quo? *Current Opinion in Neurobiology*, 20(2):156–165.

Etchell, A. C., Johnson, B. W., and Sowman, P. F. (2015). Beta oscillations, timing, and stuttering. *Frontiers in Human Neuroscience*, 8:10.3389/fnhum.2014.01036.

Etchell, A. C., Ryan, M., Martin, E., Johnson, B. W., and Sowman, P. F. (2016). Abnormal time course of low beta modulation in non-fluent preschool children: A magnetoencephalographic study of rhythm tracking. *NeuroImage*, 125:953–963.

Farmer, S. F. (1998). Rhythmicity, synchronization and binding in human and primate motor systems. *The Journal of Physiology*, 509(1):3–14.

Fitch, W. T. and Rosenfeld, A. J. (2007). Perception and Production of Syncopated Rhythms. *Music Perception: An Interdisciplinary Journal*, 25(1):43–58.

Flevaris, A. V., Bentin, S., and Robertson, L. C. (2010). Local or global? Attentional selection of spatial frequencies binds shapes to hierarchical levels. *Psychological Science*, 21(3):424–431.

Flevaris, A. V. and Robertson, L. C. (2016). Spatial frequency selection and integration of global and local information in visual processing: A selective review and tribute to Shlomo Bentin. *Neuropsychologia*, 83:192–200.

Flinker, A., Doyle, W. K., Mehta, A. D., Devinsky, O., and Poeppel, D. (2019). Spectrotemporal modulation provides a unifying framework for auditory cortical asymmetries. *Nature Human Behaviour*, 3(4):393–405.

Fontolan, L., Morillon, B., Liegeois-Chauvel, C., and Giraud, A.-L. (2014). The contribution of frequency-specific activity to hierarchical information processing in the human auditory cortex. *Nature Communications*, 5:4694.

Formaggio, E., Storti, S. F., Avesani, M., Cerini, R., Milanese, F., Gasparini, A., Acler, M., Pozzi Mucelli, R., Fiaschi, A., and Manganotti, P. (2008). EEG and fMRI Coregistration to Investigate the Cortical Oscillatory Activities During Finger Movement. *Brain Topography*, 21(2):100–111.

Franz, E. A., Eliassen, J. C., Ivry, R. B., and Gazzaniga, M. S. (1996). Dissociation of Spatial and Temporal Coupling in the Bimanual Movements of Callosotomy Patients. *Psychological Science*, 7(5):306–310.

Fujioka, T., Ross, B., and Trainor, L. J. (2015). Beta-Band Oscillations Represent Auditory Beat and Its Metrical Hierarchy in Perception and Imagery. *Journal of Neuroscience*, 35(45):15187–15198.

Fujioka, T., Trainor, L. J., Large, E. W., and Ross, B. (2012). Internalized Timing of Isochronous Sounds Is Represented in Neuromagnetic Beta Oscillations. *Journal of Neuroscience*, 32(5):1791–1802.

Fujioka, T., Zendel, B. R., and Ross, B. (2010). Endogenous Neuromagnetic Activity for Mental Hierarchy of Timing. *Journal of Neuroscience*, 30(9):3458–3466.

Fujiyama, H., Van Soom, J., Rens, G., Cuypers, K., Heise, K.-F., Levin, O., and Swinnen, S. P. (2016). Performing two different actions simultaneously: The critical role of interhemispheric interactions during the preparation of bimanual movement. *Cortex*, 77:141–154.

Funk, A. P. and Epstein, C. M. (2004). Natural rhythm: evidence for occult 40 Hz gamma oscillation in resting motor cortex. *Neuroscience Letters*, 371(2-3):181–184.

Galuske, R. A., Schlote, W., Bratzke, H., and Singer, W. (2000). Interhemispheric asymmetries of the modular structure in human temporal cortex. *Science (New York, N.Y.)*, 289(5486):1946–1949.

Gamez, J., Mendoza, G., Prado, L., Betancourt, A., and Merchant, H. (2019). The amplitude in periodic neural state trajectories underlies the tempo of rhythmic tapping. *PLOS Biology*, 17(4):e3000054.

Gazzaniga, M. S. (2000). Cerebral specialization and interhemispheric communication: does the corpus callosum enable the human condition? *Brain: A Journal of Neurology*, 123 (Pt 7):1293–1326.

Gehrig, J., Wibral, M., Arnold, C., and Kell, C. A. (2012). Setting Up the Speech Production Network: How Oscillations Contribute to Lateralized Information Routing. *Frontiers in Psychology*, 3:10.3389/fpsyg.2012.00169.

Gerloff, C. and Andres, F. G. (2002). Bimanual coordination and interhemispheric interaction. *Acta psychologica*, 110(2):161–186.

Giraud, A. L. and Truy, E. (2002). The contribution of visual areas to speech comprehension: a PET study in cochlear implants patients and normal-hearing subjects. *Neuropsychologia*, 40(9):1562–1569.

Gompf, F., Pflug, A., Laufs, H., and Kell, C. A. (2017). Non-linear Relationship between BOLD Activation and Amplitude of Beta Oscillations in the Supplementary Motor Area during Rhythmic Finger Tapping and Internal Timing. *Frontiers in Human Neuroscience*, 11:10.3389/fnhum.2017.00582.

Grahn, J. A. and Brett, M. (2007). Rhythm and Beat Perception in Motor Areas of the Brain. *Journal of Cognitive Neuroscience*, 19(5):893–906.

Grahn, J. A. and Rowe, J. B. (2009). Feeling the Beat: Premotor and Striatal Interactions in Musicians and Nonmusicians during Beat Perception. *Journal of Neuroscience*, 29(23):7540–7548.

Gross, J., Hoogenboom, N., Thut, G., Schyns, P., Panzeri, S., Belin, P., and Garrod, S. (2013). Speech Rhythms and Multiplexed Oscillatory Sensory Coding in the Human Brain. *PLOS Biology*, 11(12):e1001752.

Gross, J., Kujala, J., Hmlinen, M., Timmermann, L., Schnitzler, A., and Salmelin, R. (2001). Dynamic imaging of coherent sources: studying neural interactions in the human brain. *Proceedings of the National Academy of Sciences*, 98(2):694–699.

Gross, J., Timmermann, L., Kujala, J., Dirks, M., Schmitz, F., Salmelin, R., and Schnitzler, A. (2002). The neural basis of intermittent motor control in humans. *Proceedings of the National Academy of Sciences*, 99(4):2299–2302.

Haaland, K. Y. (2000). Neural representations of skilled movement. *Brain*, 123(11):2306–2313.

Haaland, K. Y., Elsinger, C. L., Mayer, A. R., Durgerian, S., and Rao, S. M. (2004). Motor sequence complexity and performing hand produce differential patterns of hemispheric lateralization. *Journal of Cognitive Neuroscience*, 16(4):621–636.

Haaland, K. Y. and Harrington, D. L. (1994). Limb-Sequencing Deficits After Left but not Right Hemisphere Damage. *Brain and Cognition*, 24(1):104–122.

Haaland, K. Y. and Yeo, R. A. (1989). Neuropsychological and Neuroanatomic Aspects of Complex Motor Control. In Bigler, E. D., Yeo, R. A., and Turkheimer, E., editors, *Neuropsychological Function and Brain Imaging*, Critical Issues in Neuropsychology, pages 219–244. Springer US.

Haller, M., Donoghue, T., Peterson, E., Varma, P., Sebastian, P., Gao, R., Noto, T., Knight, R. T., Shestyuk, A., and Voytek, B. (2018). Parameterizing neural power spectra. *bioRxiv*, page 299859.

Hanslmayr, S., Staresina, B. P., and Bowman, H. (2016). Oscillations and Episodic Memory: Addressing the Synchronization/Desynchronization Conundrum. *Trends in Neurosciences*, 39(1):16–25.

Hardwick, R. M., Rottschy, C., Miall, R. C., and Eickhoff, S. B. (2013). A quantitative meta-analysis and review of motor learning in the human brain. *Neuroimage*, 67:283–297.

Haslinger, B., Erhard, P., Weilke, F., Ceballos-Baumann, A. O., Bartenstein, P., von Einsiedel, H. G., Schwaiger, M., Conrad, B., and Boecker, H. (2002). The role of lateral premotorcerebellarparietal circuits in motor sequence control: a parametric fMRI study. *Cognitive Brain Research*, 13(2):159–168.

Hasnain, M. K., Fox, P. T., and Woldorff, M. G. (1998). Intersubject variability of functional areas in the human visual cortex. *Human Brain Mapping*, 6(4):301–315.

Haufe, S., Nikulin, V. V., Mller, K.-R., and Nolte, G. (2013). A critical assessment of connectivity measures for EEG data: a simulation study. *NeuroImage*, 64:120–133.

Hayashi, M. J., Saito, D. N., Aramaki, Y., Asai, T., Fujibayashi, Y., and Sadato, N. (2008). Hemispheric Asymmetry of Frequency-Dependent Suppression in the Ipsilateral Primary Motor Cortex During Finger Movement: A Functional Magnetic Resonance Imaging Study. *Cerebral Cortex*, 18(12):2932–2940.

Herdener, M., Humbel, T., Esposito, F., Habermeyer, B., Cattapan-Ludewig, K., and Seifritz, E. (2014). Jazz Drummers Recruit Language-Specific Areas for the Processing of Rhythmic Structure. *Cerebral Cortex*, 24(3):836–843.

Herrojo Ruiz, M., Brcke, C., Nikulin, V. V., Schneider, G.-H., and Khn, A. A. (2014a). Beta-band amplitude oscillations in the human internal globus pallidus support the encoding of sequence boundaries during initial sensorimotor sequence learning. *NeuroImage*, 85, Part 2:779–793.

Herrojo Ruiz, M., Rusconi, M., Brucke, C., Haynes, J.-D., Schonecker, T., and Kuhn, A. A. (2014b). Encoding of sequence boundaries in the subthalamic nucleus of patients with Parkinson's disease. *Brain*, 137(10):2715–2730.

Hickok, G. (2015). The interface theory of perception: the future of the science of the mind? *Psychonomic Bulletin & Review*, 22(6):1477–1479.

Hickok, G., Houde, J., and Rong, F. (2011). Sensorimotor integration in speech processing: computational basis and neural organization. *Neuron*, 69(3):407–422.

Hlustk, P., Solodkin, A., Gullapalli, R. P., Noll, D. C., and Small, S. L. (2002). Functional lateralization of the human premotor cortex during sequential movements. *Brain and cognition*, 49(1):54–62.

Iversen, J. R., Patel, A. D., and Ohgushi, K. (2008). Perception of rhythmic grouping depends on auditory experience. *The Journal of the Acoustical Society of America*, 124(4):2263–2271.

Iversen, J. R., Repp, B. H., and Patel, A. D. (2009). Top-down control of rhythm perception modulates early auditory responses. *Annals of the New York Academy of Sciences*, 1169:58–73.

Ivry, R. B. (1996). The representation of temporal information in perception and motor control. *Current Opinion in Neurobiology*, 6(6):851–857.

Ivry, R. B. and Lebby, P. C. (1993). Hemispheric differences in auditory perception are similar to those found in visual perception. *Psychological Science*, 4(1):41–45.

Ivry, R. B. and Richardson, T. C. (2002). Temporal Control and Coordination: The Multiple Timer Model. *Brain and Cognition*, 48(1):117–132.

Ivry, R. B. and Robertson, L. C. (1998). *The Two Sides of Perception*. MIT Press.

Jaencke, L., Loose, R., Lutz, K., Specht, K., and Shah, N. J. (2000a). Cortical activations during paced finger-tapping applying visual and auditory pacing stimuli. *Cognitive Brain Research*, 10(12):51–66.

Jaencke, L., Peters, M., Himmelbach, M., Nsselt, T., Shah, J., and Steinmetz, H. (2000b). fMRI study of bimanual coordination. *Neuropsychologia*, 38(2):164–174.

Jensen, O., Goel, P., Kopell, N., Pohja, M., Hari, R., and Ermentrout, B. (2005). On the human sensorimotor-cortex beta rhythm: sources and modeling. *Neuroimage*, 26(2):347–355.

Jones, M. R. (1987). Dynamic pattern structure in music: recent theory and research. *Perception & Psychophysics*, 41(6):621–634.

Junge, D., Rosenberg, J. R., and Halliday, D. M. (1998). Physiological tremor in human jaw-muscle system. *Archives of Oral Biology*, 43(1):45–54.

Kaiser, J., Lutzenberger, W., Preissl, H., Mosshammer, D., and Birbaumer, N. (2000). Statistical probability mapping reveals high-frequency magnetoencephalographic activity in supplementary motor area during self-paced finger movements. *Neuroscience Letters*, 283(1):81–84.

Kaminski, M., Brzezicka, A., Kaminski, J., and Blinowska, K. J. (2016). Measures of Coupling between Neural Populations Based on Granger Causality Principle. *Frontiers in Computational Neuroscience*, 10.

Karpati, F. J., Giacosa, C., Foster, N. E. V., Penhune, V. B., and Hyde, K. L. (2016). Sensorimotor integration is enhanced in dancers and musicians. *Experimental Brain Research*, 234(3):893–903.

Kell, C. A. and Keller, C. (2016). Contributions of auditory, cognitive, and motor computations to lateralization of speech processing. In *Speech Motor Control in Normal and Disordered Speech. Future Developments in Theory and Methodology*, pages 25–46. American Speech-Language-Hearing Association.

Kell, C. A., Morillon, B., Kouneiher, F., and Giraud, A.-L. (2011). Lateralization of Speech Production Starts in Sensory CorticesA Possible Sensory Origin of Cerebral Left Dominance for Speech. *Cerebral Cortex*, 21(4):932–937.

Kell, C. A., Neumann, K., Behrens, M., von Gudenberg, A. W., and Giraud, A.-L. (2018). Speaking-related changes in cortical functional connectivity associated with assisted and spontaneous recovery from developmental stuttering. *Journal of Fluency Disorders*, 55:135–144.

Kell, C. A., Neumann, K., von Kriegstein, K., Posenenske, C., von Gudenberg, A. W., Euler, H., and Giraud, A.-L. (2009). How the brain repairs stuttering. *Brain: A Journal of Neurology*, 132(Pt 10):2747–2760.

Keller, C. and Kell, C. A. (2016). Asymmetric intra- and interhemispheric interactions during covert and overt sentence reading. *Neuropsychologia*, 93(Pt B):448–465.

Keller, P. E. and Burnham, D. K. (2005). Musical Meter in Attention to Multipart Rhythm. *Music Perception: An Interdisciplinary Journal*, 22(4):629–661.

Kilavik, B. E., Zaepffel, M., Brovelli, A., MacKay, W. A., and Riehle, A. (2013). The ups and downs of beta oscillations in sensorimotor cortex. *Experimental Neurology*, 245:15–26.

Kimura, D. (1964). Left-right differences in the perception of melodies. *Quarterly Journal of Experimental Psychology*, 16(4):355–358.

Kimura, D. (1993). *Neuromotor Mechanisms in Human Communication*. Oxford University Press.

Kitterle, F. L., Christman, S., and Hellige, J. B. (1990). Hemispheric differences are found in the identification, but not the detection, of low versus high spatial frequencies. *Perception & Psychophysics*, 48(4):297–306.

Kononowicz, T. W. and Rijn, H. v. (2015). Single trial beta oscillations index time estimation. *Neuropsychologia*, 75:381–389.

Kopell, N., Ermentrout, G. B., Whittington, M. A., and Traub, R. D. (2000). Gamma rhythms and beta rhythms have different synchronization properties. *Proceedings of the National Academy of Sciences of the United States of America*, 97(4):1867–1872.

Kornysheva, K., Schubotz, R. I., and Tsakiris, M. (2011). Impairment of Auditory-Motor Timing and Compensatory Reorganization after Ventral Premotor Cortex Stimulation. *PLOS ONE*, 6(6):e21421.

Kotz, S. A., Schwartze, M., and Schmidt-Kassow, M. (2009). Non-motor basal ganglia functions: A review and proposal for a model of sensory predictability in auditory language perception. *Cortex*, 45(8):982–990.

Kotz, S. A. E. and Schwartze, Michael, M. (2011). Differential Input of the Supplementary Motor Area to a Dedicated Temporal Processing Network: Functional and Clinical Implications. *Frontiers in Integrative Neuroscience*, 5:10.3389/fnint.2011.00086.

Kujala, J., Sudre, G., Vartiainen, J., Liljestrm, M., Mitchell, T., and Salmelin, R. (2014). Multivariate analysis of correlation between electrophysiological and hemodynamic responses during cognitive processing. *NeuroImage*, 92:207–216.

Kulashekhar, S., Pekkola, J., Palva, J. M., and Palva, S. (2016). The role of cortical beta oscillations in time estimation: Oscillations in Time Estimation. *Human Brain Mapping*, 37(9):3262–3281.

Kunert, R., Willems, R. M., Casasanto, D., Patel, A. D., and Hagoort, P. (2015). Music and Language Syntax Interact in Brocas Area: An fMRI Study. *PLOS ONE*, 10(11):e0141069.

Large, E. W., Herrera, J. A., and Velasco, M. J. (2015). Neural Networks for Beat Perception in Musical Rhythm. *Frontiers in Systems Neuroscience*, 9.

Larsson, J., Gulys, B., and Roland, P. E. (1996). Cortical representation of self-paced finger movement:. *NeuroReport*, 7(2):463–468.

Laufs, H., Kleinschmidt, A., Beyerle, A., Eger, E., Salek-Haddadi, A., Preibisch, C., and Krakow, K. (2003). EEG-correlated fMRI of human alpha activity. *NeuroImage*, 19(4):1463–1476.

Lee, J. H., Whittington, M. A., and Kopell, N. J. (2013). Top-Down Beta Rhythms Support Selective Attention via Interlaminar Interaction: A Model. *PLoS Computational Biology*, 9(8):e1003164.

Leiguarda, R. C. and Marsden, C. D. (2000). Limb apraxias. *Brain*, 123(5):860–879.

Lewis, P. A. and Miall, R. C. (2002). Brain activity during non-automatic motor production of discrete multi-second intervals:. *NeuroReport*, 13(14):1731–1735.

Liepmann, H. (1905). The left hemisphere and action.(Translation from Muenchener Medizinische Wochenschrift 1905, 4849. Translations from Liepmanns essays on apraxia. *Research bulletin*, 506.

Lim, K.-B., Kim, Y.-K., Lee, H.-J., Yoo, J., Hwang, J. Y., Kim, J.-A., and Kim, S.-K. (2013). The Therapeutic Effect of Neurologic Music Therapy and Speech Language Therapy in Post-Stroke Aphasic Patients. *Annals of Rehabilitation Medicine*, 37(4):556–562.

London, J. (2012). *Hearing in time: Psychological aspects of musical meter*. Oxford University Press.

Lundqvist, M., Herman, P., and Lansner, A. (2011). Theta and Gamma Power Increases and Alpha/Beta Power Decreases with Memory Load in an Attractor Network Model. *Journal of Cognitive Neuroscience*, 23(10):3008–3020.

Luo, H., Boemio, A., Gordon, M., and Poeppel, D. (2007). The perception of FM sweeps by Chinese and English listeners. *Hearing Research*, 224(1-2):75–83.

Mars, R. B., Piekema, C., Coles, M. G. H., Hulstijn, W., and Toni, I. (2007). On the Programming and Reprogramming of Actions. *Cerebral Cortex*, 17(12):2972–2979.

Mattheson, J. (1739). *Der vollkommene Capellmeister; das ist gruendliche Anzeige aller derjenigen Sachen, die einer wissen... und vollkommen inne haben muss, der einer Capelle mit Ehren... vorstehen will: zum Versuch entworffen von Mattheson.* C. Herold.

Mayville, J. M., Fuchs, A., Ding, M., Cheyne, D., Deecke, L., and Kelso, J. A. Scott (2001). Event-related changes in neuromagnetic activity associated with syncopation and synchronization timing tasks. *Human Brain Mapping*, 14(2):65–80.

McFie, J., Piercy, M. F., and Zangwill, O. L. (1950). Visual-spatial agnosia associated with lesions of the right cerebral hemisphere. *Brain: A Journal of Neurology*, 73(2):167–190.

Meijer, D., te Woerd, E., and Praamstra, P. (2016). Timing of beta oscillatory synchronization and temporal prediction of upcoming stimuli. *NeuroImage*, 138:233–241.

Meister, I., Krings, T., Foltys, H., Boroojerdi, B., Mller, M., Tpper, R., and Thron, A. (2005). Effects of long-term practice and task complexity in musicians and nonmusicians performing simple and complex motor tasks: Implications for cortical motor organization. *Human Brain Mapping*, 25(3):345–352.

Mellet, E., Jobard, G., Zago, L., Crivello, F., Petit, L., Joliot, M., Mazoyer, B., and Tzourio-Mazoyer, N. (2014). Relationships between hand laterality and verbal and spatial skills in 436 healthy adults balanced for handedness. *Laterality: Asymmetries of Body, Brain and Cognition*, 19(4):383–404.

Merchant, H. and Honing, H. (2014). Are non-human primates capable of rhythmic entrainment? Evidence for the gradual audiomotor evolution hypothesis. *Frontiers in Neuroscience*, 7:e00274.

Merchant, H., Prez, O., Bartolo, R., Mndez, J. C., Mendoza, G., Gmez, J., Yc, K., and Prado, L. (2015). Sensorimotor neural dynamics during isochronous tapping in the medial premotor cortex of the macaque. *European Journal of Neuroscience*, 41(5):586–602.

Merchant, H., Prez, O., Zarco, W., and Gmez, J. (2013). Interval tuning in the primate medial premotor cortex as a general timing mechanism. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 33(21):9082–9096.

Minagawa-Kawai, Y., Cristi, A., and Dupoux, E. (2011). Cerebral lateralization and early speech acquisition: a developmental scenario. *Developmental Cognitive Neuroscience*, 1(3):217–232.

Minagawa-Kawai, Y., Mori, K., Naoi, N., and Kojima, S. (2007). Neural Attunement Processes in Infants during the Acquisition of a Language-Specific Phonemic Contrast. *Journal of Neuroscience*, 27(2):315–321.

Morillon, B. and Baillet, S. (2017). Motor origin of temporal predictions in auditory attention. *Proceedings of the National Academy of Sciences of the United States of America*, 114(42):E8913–E8921.

Morillon, B., Hackett, T. A., Kajikawa, Y., and Schroeder, C. E. (2015). Predictive motor control of sensory dynamics in auditory active sensing. *Current Opinion in Neurobiology*, 31:230–238.

Morillon, B., Kell, C. A., and Giraud, A.-L. (2009). Three Stages and Four Neural Systems in Time Estimation. *Journal of Neuroscience*, 29(47):14803–14811.

Morillon, B., Schroeder, C. E., and Wyart, V. (2014). Motor contributions to the temporal precision of auditory attention. *Nature Communications*, 5:5255.

Morillon, B., Schroeder, C. E., Wyart, V., and Arnal, L. H. (2016). Temporal Prediction in lieu of Periodic Stimulation. *The Journal of Neuroscience*, 36(8):2342–2347.

Mottonen, R., Ven, G. M. v. d., and Watkins, K. E. (2014). Attention Fine-Tunes Auditory-Motor Processing of Speech Sounds. *Journal of Neuroscience*, 34(11):4064–4069.

Murakami, T., Kell, C. A., Restle, J., Ugawa, Y., and Ziemann, U. (2015). Left Dorsal Speech Stream Components and Their Contribution to Phonological Processing. *Journal of Neuroscience*, 35(4):1411–1422.

Muthuraman, M., Hellriegel, H., Hoogenboom, N., Anwar, A. R., Mideksa, K. G., Krause, H., Schnitzler, A., Deuschl, G., and Raethjen, J. (2014). Beamformer Source Analysis and Connectivity on Concurrent EEG and MEG Data during Voluntary Movements. *PLOS ONE*, 9(3):e91441.

Muthuraman, M., Raethjen, J., Koirala, N., Anwar, A. R., Mideksa, K. G., Elble, R., Groppa, S., and Deuschl, G. (2018). Cerebello-cortical network fingerprints differ between essential, Parkinson's and mimicked tremors. *Brain: A Journal of Neurology*, 141(6):1770–1781.

Muthuraman, M., Tams, G., Hellriegel, H., Deuschl, G., and Raethjen, J. (2012). Source analysis of beta-synchronisation and cortico-muscular coherence after movement termination based on high resolution electroencephalography. *PloS One*, 7(3):e33928.

Nalatore, H., Ding, M., and Rangarajan, G. (2007). Mitigating the effects of measurement noise on Granger causality. *Physical Review. E, Statistical, Nonlinear, and Soft Matter Physics*, 75(3 Pt 1):031123.

Navon, D. (1977). Forest before trees: The precedence of global features in visual perception. *Cognitive Psychology*, 9(3):353–383.

Neef, N. E., Hoang, T. N. Linh, Neef, A., Paulus, W., and Sommer, M. (2015). Speech dynamics are coded in the left motor cortex in fluent speakers but not in adults who stutter. *Brain: A Journal of Neurology*, 138(Pt 3):712–725.

Neuper, C. and Pfurtscheller, G. (2001). Evidence for distinct beta resonance frequencies in human EEG related to specific sensorimotor cortical areas. *Clinical Neurophysiology*, 112(11):2084–2097.

Nobre, A., Correa, A., and Coull, J. (2007). The hazards of time. *Current Opinion in Neurobiology*, 17(4):465–470.

Nozaradan, S., Peretz, I., and Mouraux, A. (2012). Selective Neuronal Entrainment to the Beat and Meter Embedded in a Musical Rhythm. *Journal of Neuroscience*, 32(49):17572–17581.

Nozaradan, S., Zerouali, Y., Peretz, I., and Mouraux, A. (2015). Capturing with EEG the Neural Entrainment and Coupling Underlying Sensorimotor Synchronization to the Beat. *Cerebral Cortex*, 25(3):736–747.

Ohara, S. (2000). Movement-related change of electrocorticographic activity in human supplementary motor area proper. *Brain*, 123(6):1203–1215.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, 9(1):97–113.

Oostenveld, R., Fries, P., Maris, E., and Schoffelen, J.-M. (2011). FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data. *Computational Intelligence and Neuroscience*, 2011:1–9.

Parncutt, R. and Cohen, A. J. (1995). Identification of microtonal melodies: effects of scale-step size, serial order, and training. *Perception & Psychophysics*, 57(6):835–846.

Peters, M. (1980). Why the preferred hand taps more quickly than the non-preferred hand: Three experiments on handedness. *Canadian Journal of Psychology/Revue canadienne de psychologie*, 34(1):62–71.

Peters, M. (1985). Constraints in the performance of bimanual tasks and their expression in unskilled and skilled subjects. *The Quarterly Journal of Experimental Psychology Section A*, 37(2):171–196.

Peters, M. (1987). A nontrivial motor performance difference between right-handers and left-handers: Attention as intervening variable in the expression of handedness. *Canadian Journal of Experimental Psychology*, 41:91.

Peters, M. and Durding, B. (1979). Left-handers and right-handers compared on a motor task. *Journal of Motor Behavior*, 11(2):103–111.

Peters, M. and Schwartz, S. (1989). Coordination of the two hands and effects of attentional manipulation in the production of a bimanual 2:3 polyrhythm. *Australian Journal of Psychology*, 41(2):215–224.

Pflug, A., Gompf, F., and Kell, C. A. (2017). Bimanual tapping of a syncopated rhythm reveals hemispheric preferences for relative movement frequencies. *Human Movement Science*, 54:287–296.

Pflug, A., Gompf, F., Muthuraman, M., Groppa, S., and Kell, C. A. (2019). Differential contributions of the two human cerebral hemispheres to action timing. *eLife*, 8:e48404.

Pfurtscheller, G. (1981). Central beta rhythm during sensorimotor activities in man. *Electroencephalography and Clinical Neurophysiology*, 51(3):253–264.

Pfurtscheller, G. and Lopes da Silva, F. H., editors (1999). *Event-related desynchronization.* Number rev. ser. v. 6 in Handbook of electroencephalography and clinical neurophysiology. Elsevier, New York ; Amsterdam, 1st ed edition.

Pfurtscheller, G., Woertz, M., Supp, G., and Lopes da Silva, F. (2003). Early onset of post-movement beta electroencephalogram synchronization in the supplementary motor area during self-paced finger movement in man. *Neuroscience Letters*, 339(2):111–114.

Picazio, S., Veniero, D., Ponzo, V., Caltagirone, C., Gross, J., Thut, G., and Koch, G. (2014). Prefrontal Control over Motor Cortex Cycles at Beta Frequency during Movement Inhibition. *Current Biology*, 24(24):2940–2945.

Poeppel, D. (2003). The analysis of speech in different temporal integration windows: cerebral lateralization as asymmetric sampling in time. *Speech Communication*, 41(1):245–255.

Pollok, B., Gross, J., Mller, K., Aschersleben, G., and Schnitzler, A. (2005). The cerebral oscillatory network associated with auditorily paced finger movements. *NeuroImage*, 24(3):646–655.

Povel, D.-J. and Essens, P. (1985). Perception of Temporal Patterns. *Music Perception: An Interdisciplinary Journal*, 2(4):411–440.

Rao, S. M., Binder, J. R., Bandettini, P. A., Hammeke, T. A., Yetkin, F. Z., Jesmanowicz, A., Lisk, L. M., Morris, G. L., Mueller, W. M., Estkowski, L. D., Wong, E. C., Haughton, V. M., and Hyde, J. S. (1993). Functional magnetic resonance imaging of complex human movements. *Neurology*, 43(11):2311–2311.

Rao, S. M., Harrington, D. L., Haaland, K. Y., Bobholz, J. A., Cox, R. W., and Binder, J. R. (1997). Distributed neural systems underlying the timing of movements. *Journal of Neuroscience*, 17(14):5528–5535.

Repp, B. H. (2003). Rate Limits in Sensorimotor Synchronization With Auditory and Visual Sequences: The Synchronization Threshold and the Benefits and Costs of Interval Subdivision. *Journal of motor behavior*, 35(4):355–370.

Repp, B. H. (2005). Sensorimotor synchronization: A review of the tapping literature. *Psychonomic Bulletin & Review*, 12(6):969–992.

Repp, B. H. (2010). Self-Generated Interval Subdivision Reduces Variability of Synchronization with a Very Slow Metronome. *Music Perception*, 27(5):389–397.

Repp, B. H. and Su, Y.-H. (2013). Sensorimotor synchronization: A review of recent research (20062012). *Psychonomic Bulletin & Review*, 20(3):403–452.

Rhodes, B. J., Bullock, D., Verwey, W. B., Averbeck, B. B., and Page, M. P. A. (2004). Learning and production of movement sequences: Behavioral, neurophysiological, and modeling perspectives. *Human Movement Science*, 23(5):699–746.

Riecker, A., Mathiak, K., Wildgruber, D., Erb, M., Hertrich, I., Grodd, W., and Ackermann, H. (2005). fMRI reveals two distinct cerebral networks subserving speech motor control. *Neurology*, 64(4):700–706.

Ringo, J. L., Doty, R. W., Demeter, S., and Simard, P. Y. (1994). Time Is of the Essence: A Conjecture that Hemispheric Specialization Arises from Interhemispheric Conduction Delay. *Cerebral Cortex*, 4(4):331–343.

Ritter, P., Moosmann, M., and Villringer, A. (2009). Rolandic alpha and beta EEG rhythms' strengths are inversely related to fMRI-BOLD signal in primary somatosensory and motor cortex. *Human Brain Mapping*, 30(4):1168–1187.

Robertson, L. C. and Ivry, R. (2000). Hemispheric Asymmetries: Attention to Visual and Auditory Primitives. *Current Directions in Psychological Science*, 9(2):59–63.

Roelfsema, P. R., Engel, A. K., Knig, P., and Singer, W. (1997). Visuomotor integration is associated with zero time-lag synchronization among cortical areas. *Nature*, 385(6612):157–161.

Roopun, A. K., Middleton, S. J., Cunningham, M. O., LeBeau, F. E. N., Bibbig, A., Whittington, M. A., and Traub, R. D. (2006). A beta2-frequency (20-30 Hz) oscillation in nonsynaptic networks of somatosensory cortex. *Proceedings of the National Academy of Sciences*, 103(42):15646–15650.

Ross, B. and Tremblay, K. (2009). Stimulus experience modifies auditory neuromagnetic responses in young and older listeners. *Hearing Research*, 248(1-2):48–59.

Ruitenberg, M. F. L., Verwey, W. B., and Abrahamse, E. L. (2015). What determines the impact of context on sequential action? *Human Movement Science*, 40:298–314.

Rushworth, M., Johansen-Berg, H., Gbel, S., and Devlin, J. (2003). The left parietal and premotor cortices: motor attention and selection. *NeuroImage*, 20:S89–S100.

Sainburg, R. L. (2002). Evidence for a dynamic-dominance hypothesis of handedness. *Experimental Brain Research*, 142(2):241–258.

Salmelin, R., Hmalinen, M., Kajola, M., and Hari, R. (1995). Functional Segregation of Movement-Related Rhythmic Activity in the Human Brain. *NeuroImage*, 2(4):237–243.

Scheeringa, R., Fries, P., Petersson, K.-M., Oostenveld, R., Grothe, I., Norris, D. G., Hagoort, P., and Bastiaansen, M. C. (2011). Neuronal Dynamics Underlying High- and Low-Frequency EEG Oscillations Contribute Independently to the Human BOLD Signal. *Neuron*, 69(3):572–583.

Scheeringa, R., Petersson, K. M., Oostenveld, R., Norris, D. G., Hagoort, P., and Bastiaansen, M. C. (2009). Trial-by-trial coupling between EEG and BOLD identifies networks related to alpha and theta EEG power increases during working memory maintenance. *NeuroImage*, 44(3):1224–1238.

Schluter, N., Krams, M., Rushworth, M., and Passingham, R. (2001). Cerebral dominance for action in the human brain: the selection of actions. *Neuropsychologia*, 39(2):105–113.

Schroeder, C. E. and Lakatos, P. (2009). Low-frequency neuronal oscillations as instruments of sensory selection. *Trends in Neurosciences*, 32(1):9–18.

Schubotz, R. I. (2007). Prediction of external events with our motor system: towards a new framework. *Trends in Cognitive Sciences*, 11(5):211–218.

Schubotz, R. I., Friederici, A. D., and Yves von Cramon, D. (2000). Time Perception and Motor Timing: A Common Cortical and Subcortical Basis Revealed by fMRI. *NeuroImage*, 11(1):1–12.

Schwartze, M., Tavano, A., Schrger, E., and Kotz, S. A. (2012). Temporal aspects of prediction in audition: Cortical and subcortical neural mechanisms. *International Journal of Psychophysiology*, 83(2):200–207.

Sclocco, R., Tana, M. G., Visani, E., Gilioli, I., Panzica, F., Franceschetti, S., Cerutti, S., and Bianchi, A. M. (2014). EEG-informed fMRI analysis during a hand grip task: estimating the relationship between EEG rhythms and the BOLD signal. *Frontiers in Human Neuroscience*, 8.

Semjen, A. and Summers, J. J. (2002). Timing goals in bimanual coordination. *The Quarterly Journal of Experimental Psychology Section A*, 55(1):155–171.

Serrien, D. J., Cassidy, M. J., and Brown, P. (2003). The importance of the dominant hemisphere in the organization of bimanual movements. *Human Brain Mapping*, 18(4):296–305.

Serrien, D. J., Ivry, R. B., and Swinnen, S. P. (2006). Dynamics of hemispheric specialization and integration in the context of motor control. *Nature Reviews. Neuroscience*, 7(2):160–166.

Serrien, D. J., Sovijarvi-Spape, M. M., and Farnsworth, B. (2012). Bimanual control processes and the role of handedness. *Neuropsychology*, 26(6):802–807.

Serrien, D. J. and Sovijrvi-Spap, M. M. (2015). Hemispheric asymmetries and the control of motor sequences. *Behavioural Brain Research*, 283:30–36.

Shankweiler, D. (1966). Effects of temporal-lobe damage on perception of dichotically presented melodies. *Journal of Comparative and Physiological Psychology*, 62(1):115–119.

Shankweiler, D. and Studdert-Kennedy, M. (1967). Identification of consonants and vowels presented to left and right ears. *The Quarterly Journal of Experimental Psychology*, 19(1):59–63.

Steinstraeter, O., Teismann, I. K., Wollbrink, A., Suntrup, S., Stoeckigt, K., Dziewas, R., and Pantev, C. (2009). Local sphere-based co-registration for SAM group analysis in subjects without individual MRI. *Experimental Brain Research*, 193(3):387–396.

Stephan, K. E., Marshall, J. C., Friston, K. J., Rowe, J. B., Ritzl, A., Zilles, K., and Fink, G. R. (2003). Lateralized cognitive processes and lateralized task control in the human brain. *Science (New York, N.Y.)*, 301(5631):384–386.

Swinnen, S. P. (2002). Intermanual coordination: From behavioural principles to neural-network interactions. *Nature Reviews Neuroscience*, 3(5):348–359.

Swinnen, S. P. and Wenderoth, N. (2004). Two hands, one brain: cognitive neuroscience of bimanual skill. *Trends in Cognitive Sciences*, 8(1):18–25.

Tamas, G., Chirumamilla, V. C., Anwar, A. R., Raethjen, J., Deuschl, G., Groppa, S., and Muthuraman, M. (2018). Primary Sensorimotor Cortex Drives the Common Cortical Network for Gamma Synchronization in Voluntary Hand Movements. *Frontiers in Human Neuroscience*, 12:130.

Thaler, D., Chen, Y. C., Nixon, P. D., Stern, C. E., and Passingham, R. E. (1995). The functions of the medial premotor cortex. *Experimental Brain Research*, 102(3):445–460.

Thaut, M. H. and McIntosh, G. C. (2014). Neurologic Music Therapy in Stroke Rehabilitation. *Current Physical Medicine and Rehabilitation Reports*, 2(2):106–113.

Toga, A. W. and Thompson, P. M. (2003). Mapping brain asymmetry. *Nature Reviews. Neuroscience*, 4(1):37–48.

Tsapeli, F. and Musolesi, M. (2015). Investigating Causality in Human Behavior from Smartphone Sensor Data: A Quasi-Experimental Approach. *EPJ Data Science*, 4(1). arXiv: 1505.02818.

Tuller, B. and Kelso, J. A. S. (1989). Environmentally-specified patterns of movement coordination in normal and split-brain subjects. *Experimental Brain Research*, 75(2):306–316.

Tzourio-Mazoyer, N. (2016). Intra- and Inter-hemispheric Connectivity Supporting Hemispheric Specialization. In Kennedy, H., Van Essen, D. C., and Christen, Y., editors, *Micro-, Meso- and Macro-Connectomics of the Brain*. Springer, Cham (CH).

van Atteveldt, N., Murray, M. M., Thut, G., and Schroeder, C. E. (2014). Multisensory integration: flexible use of general operations. *Neuron*, 81(6):1240–1253.

Van Veen, B., Van Drongelen, W., Yuchtman, M., and Suzuki, A. (1997). Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. *IEEE Transactions on Biomedical Engineering*, 44(9):867–880.

Verwey, W. B. (1999). Evidence for a multistage model of practice in a sequential movement task. *Journal of Experimental Psychology: Human Perception and Performance*, 25(6):1693–1708.

von Stein, A. (1999). Synchronization Between Temporal and Parietal Cortex During Multimodal Object Processing in Man. *Cerebral Cortex*, 9(2):137–150.

von Wegner, F., Tagliazucchi, E., Brodbeck, V., and Laufs, H. (2016). Analytical and empirical fluctuation functions of the EEG microstate random walk - Short-range vs. long-range correlations. *NeuroImage*, 141:442–451.

Vuust, P., Pallesen, K. J., Bailey, C., van Zuijen, T. L., Gjedde, A., Roepstorff, A., and stergaard, L. (2005). To musicians, the message is in the meter: Pre-attentive neuronal responses to incongruent rhythm are left-lateralized in musicians. *NeuroImage*, 24(2):560–564.

Vuust, P., Roepstorff, A., Wallentin, M., Mouridsen, K., and stergaard, L. (2006). It don't mean a thing: Keeping the rhythm during polyrhythmic tension, activates language areas (BA47). *NeuroImage*, 31(2):832–841.

Wada, J. A., Clarke, R., and Hamm, A. (1975). Cerebral hemispheric asymmetry in humans. Cortical speech zones in 100 adults and 100 infant brains. *Archives of Neurology*, 32(4):239–246.

Wan, E. A. and Merwe, R. v. d. (2002). The Unscented Kalman Filter. In *Kalman Filtering and Neural Networks*, pages 221–280. John Wiley & Sons, Ltd.

Wang, J., Narain, D., Hosseini, E. A., and Jazayeri, M. (2018). Flexible timing by temporal scaling of cortical responses. *Nature Neuroscience*, 21(1):102–110.

Wang, L. E., Fink, G. R., Diekhoff, S., Rehme, A. K., Eickhoff, S. B., and Grefkes, C. (2011). Noradrenergic enhancement improves motor network connectivity in stroke patients. *Annals of Neurology*, 69(2):375–388.

Wiener, M., Turkeltaub, P., and Coslett, H. (2010). The image of time: A voxel-wise meta-analysis. *NeuroImage*, 49(2):1728–1740.

Witt, S. T., Laird, A. R., and Meyerand, M. E. (2008). Functional neuroimaging correlates of finger-tapping task variations: An ALE meta-analysis. *NeuroImage*, 42(1):343–356.

Worsley, K. and Friston, K. (1995). Analysis of fMRI Time-Series RevisitedAgain. *NeuroImage*, 2(3):173–181.

Young, D. E., Cohen, M. J., and Husak, W. S. (1993). Contextual interference and motor skill acquisition: On the processes that influence retention. *Human Movement Science*, 12(5):577–600.

Yuan, H., Liu, T., Szarkowski, R., Rios, C., Ashe, J., and He, B. (2010). Negative covariation between task-related responses in alpha/beta-band activity and BOLD in human sensorimotor cortex: An EEG and fMRI study of motor imagery and movements. *NeuroImage*, 49(3):2596–2606.

Zanone, P. G. and Kelso, J. A. S. (1992). Learning and transfer as dynamical paradigms for behavioral change. In *Tutorials in motor behavior, 2.*, Advances in psychology, Vol. 87, pages 563–582. North-Holland, Oxford, England.

7 German summary

Das menschliche Gehirn besteht aus zwei Hemisphären. Obwohl die meisten neuronalen Funktionen auf beiden Hemisphären repräsentiert sind, scheint es Unterschiede in deren Verarbeitung zu geben, besonders bei Funktionen, die für den Menschen charakteristisch sind - Sprache und Händigkeit. Beide Funktionen lateralisieren auf der linken Hemisphäre. Aber woher kommen diese Unterschiede? Die Double-filtering-by-frequency (DFF) Theorie (Ivry and Robertson, 1998; Flevaris et al., 2010) beschreibt individuelle Präferenzen der Hemisphären bei der Selektion relativer Frequenzen von sensorischen Informationen, wobei die linke Hemisphäre die hochfrequenten und die rechte Hemisphäre die niederfrequenten Informationen verarbeitet. Die Autoren gehen davon aus, dass die in der Sensorik gefundenen Effekte auch auf die Funktionen der Sprache und Motorik übertragen werden können (Robertson and Ivry, 2000). Das Ziel dieser Arbeit war, eine Übertragbarkeit der Hypothese auf die Kontrolle von Handmotorik zu testen. Daten von gesunden Probanden wurden mit Hilfe der funktionellen Bildgebung (fMRT) und der Magnetencephalographie (MEG) erhoben, um folgende Fragen zu beantworten: Zeigen sich Effekte von hemisphärischen Präferenzen in den Verhaltensdaten und wenn ja, welche korticalen und neuronalen Mechanismen liegen diesen zu Grunde?

In einem ersten Verhaltensexperiment (Pflug et al., 2017) wurde untersucht, ob sich die linke und die rechte Hand in ihrer zeitlichen Präzision unterscheiden wenn sie schnelle bzw. langsame Rhythmen tippen. Beim schnellen Rhythmus mussten alle Probanden auf jeden Klicklaut eines kontinuierlichen auditorischen Signals (Beat) tippen, der langsame Rhythmus wurde zwischen zwei Versuchsgruppen variiert. Während die erste Gruppe einen Standard Viervierteltakt (tippen auf eins) tippte, mussten Probanden aus der zweiten Gruppe

einen synkopierten Rhythmus tippen (tippen auf vier). Die Probanden wurden gebeten entweder mit beiden Händen die gleiche Geschwindigkeit (monofrequent) oder mit einer Hand langsam und mit der anderen schnell (multifreqent) zu tippen. Im Einklang mit der DFF-Theorie war in beiden Gruppen die rechte Hand besser im Tippen der schnellen Frequenz. Ein Unterschied ergab sich im Tippen der langsamen Frequenz. Hier war die linke Hand besser im Tippen der langsamen Frequenz, aber nur in der Gruppe, die den synkopierten Rhythmus tippte. Die Ergebnisse weisen darauf hin, dass im synkopierten Paradigma beide Rhythmen getrennt voneinander in verschiedenen Hemispheren representiert werden, während im standard Viervierteltakt die Rhythmen zu einer Gestalt integriert werden.
Das synkopierte Paradigma wurde daraufhin verwendet, um im MEG und fMRT die neuralen Grundlagen dieser frequenzabhängigen Präferenzen zu untersuchen (Pflug et al., 2019). Die interne Generierung des langsamen Rhythmus führte zu einem Anstieg der BOLD-Aktivierung in der supplementorischen motorischen Rinde (SMA) und dem rechten auditorischen Assoziationskortex (A2). Die Ergebnisse des MEGs ergaben, dass im rechten A2 der langsame Ryhthmus in der Modulation des Beta-Bandes stärker representiert wurde, als im linken A2. Zusätzlich fand sich eine ausgeprägtere Representation des schnellen Klicklautes im linken A2, obwohl beide A2 den gleichen auditorischen Eingang erhalten hatten. Die Ergebnisse aus beiden Messungen legen nahe, dass die gefundenen Effekte in den sensorischen Areale die frequenzabhänginge Lateralisierung erklären können und hiermit die DFF-Hypothese auch in der Handmotorik bestätigen. Im Gegenteil zu den sensorischen Arealen representierten die motorischen Areale nur den jeweils getippten Rhythmus in Form einer Beta-Power Modulation die nicht-linear mit der BOLD-Aktivierung verknüpft war (Gompf et al., 2017). Eine ausgeprägtere Kommunikation des linken A2 mit der SMA begünstigt

eine Transformation von zwei getrennten Rhythmen in eine integrierte Gestaltrepresentation. Der gefundene Mechanismus könnte eventuell auch erklären, wie eine Lateralisierung in der Sprachprozessierung funktioniert.

Eidesstattliche Erklaerung

Ich erkläre hiermit ehrenwörtlich, dass ich die vorliegende Arbeit entsprechend den Regeln guter wissenschaftlicher Praxis selbstständig und ohne unzulässige Hilfe Dritter angefertigt habe.
Sämtliche aus fremden Quellen direkt oder indirekt übernommenen Gedanken sowie sämtliche von Anderen direkt oder indirekt übernommenen Daten, Techniken und Materialien sind als solche kenntlich gemacht. Die Arbeit wurde bisher bei keiner anderen Hochschule zu Prüfungszwecken eingereicht.

Darmstadt, den

_____

(Anja Pflug)

Anja Pflug
anja.pflug@
musterkind.eu
06151 / 950 3770
0151 / 22 19 06 71

Address
Klappacher Str. 14
64285 Darmstadt

Curriculum Vitae

Personal details

Date of birth:	22.01.1980
Marital status:	Married with two children

Working experience

05/2017 – 11/2019	Senior Data Scientist at AGT International
10/2011 – 09/2013	Research associate at University Hospital Ffm
02/2009 – 08/2010	Research associate at MPI for Brain Research
10/2005 – 04/2007	Working student at RCC-Cytotest Cell Research
01/2005 – 06/2005	Working student at Fraunhofer LBF, Darmstadt
12/2002 – 09/2003	Working student at Taunus BKK, Darmstadt
03/2002 – 09/2001	Cafe Rossi, Heidelberg

Education

since 10/2013 ***PhD Student - Biology***
Goethe University Frankfurt, Department of Neurology/ Technical University of Darmstadt
Supervisor PD C. Kell/Prof R. Galuske

since 10/2009 ***Master Student - Technology and Philosophy***
Technical University of Darmstadt

09/2007 – 08/2008 ***Diploma Student - Biology***
MPI for Biological Cybernetics/ Technical University of Darmstadt
Supervisor PD M.Munk /Prof R. Galuske

08/1999 – 01/2002 ***Education in the hotel business***
Hardtwald Hotel Bad Homburg

08/1990 – 06/1999 ***University-entrance diploma***
Philipp-Reis-Schule Friedrichsdorf

Tools

Programming Languages: Python, Matlab, Kotlin, SAS, C, R
Frameworks: Pandas, sklearn, keras, scipy, matplotlib, seaborn, librosa
Front end: HTML, LaTeX, XML in Android
Workflow: Git, Kanban, Scrum
Designing: Photoshop, Illustrator
Analytics: Machine Learning, signal processing, source reconstruction, linear and non-linear connectivity analysis, deep learning

Anja Pflug
anja.pflug@
musterkind.eu
06151 / 950 3770
0151 / 22 19 06 71

Address
Klappacher Str. 14
64285 Darmstadt

Publications

Pflug, Anja; Gompf, Florian; Muthuraman, Muthuraman; Groppa, Sergiu; Kell, Christian A. (2019): Differential contributions of the two human cerebral hemispheres to action timing. *eLife: In press*.

Gompf, Florian; Pflug, Anja; Laufs, Helmut; Kell, Christian A. (2017): Non-linear Relationship between BOLD Activation and Amplitude of Beta Oscillations in the Supplementary Motor Area during Rhythmic Finger Tapping and Internal Timing, *Frontiers in human neuroscience*. doi.org/10.3389/fnhum.2017.00582

Pflug, Anja; Gompf, Florian; Kell, Christian Alexander (2017): Bimanual tapping of a syncopated rhythm reveals hemispheric preferences for relative movement frequencies, *Human Movement Science*. Volume 54, August 2017, Pages 287-296

Lorenz, Matthias W.; Abdi, Negin Ashtiani; Scheckenbach, Frank; Pflug, Anja; Bulbul, Alpaslan; Catapano, Alberico L. et al. (2017): Automatic identification of variables in epidemiological datasets using logic regression, *BMC medical informatics and decision making*. 17, Article number: 40

Lorenz et al. (2015). Carotid intima-media thickness progression and risk of vascular events in people with diabetes: results from the PROG-IMT collaboration, *Diabetes Care*). 38(10): 1921-1929.